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Re-Medicalizing Cannabis: Science, Medicine and Policy, 1973 to the Early Twenty-First Century

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PhD.

Declaration

I, Suzanne Taylor, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Suzanne Taylor

Abstract

When cannabis-based medicine was withdrawn in the UK in 1973 it appeared cannabis' career as a medicine had ended, but even as cannabis became regulated solely as an illicit drug, it appeared it was being re-medicalized. This thesis, framed as a history of science and policy-making, studied cannabis' re-medicalization from 1973 and in so doing analysed the process whereby boundaries shift between illicit 'drug' and licit 'medicine' and the issues and interests involved.

It argues that changing scientific knowledge, from the synthesis of THC to the discovery of the endocannabinoid system, spurred by individual scientists, developing scientific disciplines, and advances in technology all contributed to a shifting environment around cannabis and opened-up new avenues for cannabis as a medicine. Initially, interest and funding were directed to the cannabis field through political and social fears over cannabis' recreational. Driven by drug control imperatives expert committees, in particular, the working groups of the Advisory Council on the Misuse of Drugs provided an early arena for discussion and stimulated research on cannabis which led ultimately to increased research on medical applications. The study reveals that although international and domestic drug control systems acted as countervailing forces, they provided spurs to re-medicalization as pressure mounted to isolate calls for medical cannabis from legalization arguments. In transforming the concept of cannabis, the drug, into cannabis, the medicine, the pharmaceutical industry was fundamental, through the provision of synthetic cannabinoids and finally plant extracts with the development of GW Pharmaceuticals and their product Sativex. The incentive to study cannabis as a medicine would not have emerged, as it did, without user activism and the thesis argues that in the UK it was pressure from Multiple Sclerosis sufferers that encouraged research and its direction. Once legitimacy was conferred by influential professional bodies, such as the BMA, and the House of Lords there was a concerted effort to place cannabis into the clinical trial system and through regulatory processes. Re-medicalization could exist within the drug control system and discourse shifted towards the drug control framework and the relative positions of both licit and illicit drugs.

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Abbreviations

ACDD	Advisory Council on Drug Dependence
ACMD	Advisory Council on the Misuse of Drugs
ACT	Alliance for Cannabis Therapeutics
AIDS	Acquired Immune Deficiency Syndrome
ARM	Annual Representative Meeting of the BMA
BMA	British Medical Association
CAMS	Cannabinoids in Multiple Sclerosis
CANPOP	Cannabis for acute post-operative pain
CBD	Cannabidiol
CBME	Cannabis-based medicine extract
CBN	Cannabinol
CND	Commission on Narcotic Drugs (UN)
CUPID	Cannabinoid use in progressive inflammatory brain disease
DDA	Dangerous Drugs Act
ECRS	Endogenous cannabinoid receptor system
FDA	Federal Drugs Administration
INCB	International Narcotics Control Bureau
MCA	Medicines Control Agency
MDA	Misuse of Drugs Act
MRC	Medical Research Council
MS	Multiple Sclerosis
NCE	New chemical entity
NIDA	National Institute of Drug Abuse
NIMH	National Institutes of Mental Health
PLR	Product Licence of Right.
RCT	Randomized Controlled Trial
THC	Tetrahyrocannabinol
WHO	World Health Organisation

Introduction

‘Britain’s drugs crisis: Recipe for dangerous medicine.’¹

The psychiatrists Griffith Edwards and John Strang used this catchy headline in 1994 to make their case for the maintenance of the drug control system and to emphasize the dangers of drug legalization. However, the phrase could apply equally to cannabis in its role as a therapeutic within the drug control framework. Cannabis is a complex substance, both because of its own structure and the baggage that it carries. The position of cannabis in society has been determined by different stakeholders at different times, each claiming different roles for the plant. In the twentieth century cannabis constituted a headache for both medical and illicit drug regulators. Its multifaceted and fluid role has meant that cannabis proved difficult to classify definitively and yet its relationship to other drugs, medical and recreational, is important as its borderline position acts as a spotlight onto drug policy.

Cannabis was introduced to the UK as a medical product in the nineteenth century. Questions quickly emerged over its safety, efficacy and its relative position, in terms of harm, to other drugs. However, as it was not widely used as a medicine or even recreationally, and it quickly became caught up in developing drug legislation aimed at more widely used drugs like opium. Its medical role had diminished by the 1950s and cannabis became viewed mainly as a drug of misuse as regulation around medical and recreational drugs was tightened. Both frameworks were in flux and their development eroded cannabis’ role as a medical product. In 1961 cannabis was brought under the control of the UN Single Convention on Narcotic Substances. The convention introduced four Schedules into which drugs were classified, with Schedule I and IV the most stringent. Cannabis and cannabis resin along with heroin were listed in Schedule I and Schedule IV, which entitled parties to adopt ‘special measures of control’, and to ban them altogether apart from medical or scientific research. Cannabis, in the form of extracts or tinctures, was placed in the slightly less restrictive Schedule I alongside morphine. The UK ratified this convention and the Dangerous Drugs Act

of 1964 enacted the provisions necessary for compliance and created the offence of the cultivation of cannabis. This was succeeded by subsequent Dangerous Drugs Acts (DDA) such as the DDA of 1965 which consolidated previous acts and the DDA of 1967 which introduced policies of stop and search. Many drugs had dual structures and drugs within the Act could be made available as medicines as there existed some overlap between controlled illicit drugs and the regulation of medicines. Cannabis as a medicine was still permissible and when the 1968 Medicines Control Act was introduced, extracts of cannabis, in the form of tinctures were made available on prescription via a 'product licence of right', (PLR). However, in the 1970s cannabis lost its dual structure. In 1971 the UN Convention on Psychotropic Substances consolidated previous legislation and incorporated emergent synthetic psychotropic drugs. Cannabis-based drugs were placed in Schedule I which included substances that had no, or very limited, medical value. Cannabis remained controlled under the Single Convention.²

These conventions were open to interpretation and parties to the conventions, such as the UK, US and Holland, took different approaches to drug control. The US domestic legislation, for example, excluded medical use for substances listed in Schedule I of their domestic Controlled Substances Act, although the international conventions permitted limited use. The Misuse of Drugs Act of 1971 was enacted in the UK and introduced the term 'controlled drugs.' The main purpose of the Act was to prevent the misuse of controlled drugs and it imposed a complete ban on the possession, supply, manufacture, import and export of controlled drugs except as allowed by regulations or by licence from the Secretary of State. It introduced the statutory body, the Advisory Council on the Misuse of Drugs (ACMD) to advise government. Schedule II of the Act identified the drugs that were to be controlled and these were divided into three classes: A, B and C. The level of classification determined the gravity of penalties that could be imposed under criminal law for an infringement of the Act. Drugs derived from cannabis, for example, cannabinoids such as cannabidiol (CBD) and THC were placed in Class A. Cannabis and cannabis resin were listed as Class B, which enabled cannabis to be used under licence from the Home Office for research purposes or for clinical trials with permission from the Medicines Control Agency. Regulations to the Act permitted exemptions for legitimate activities such as the medical use of controlled

drugs but the medical chest was stripped of the last remaining cannabis ingredient when these came into force.³ When the 'product licences of right' were reviewed by the Medicines Control Agency, cannabis' licence was not renewed and when the original regulations of the Misuse of Drugs Act were enacted in 1973 cannabis was placed in Schedule 4, now Schedule I of Misuse of Drugs Regulations, which comprised of substances with no known or limited medical use, and was therefore not exempted under the regulations. Cannabis, in any form, could no longer be prescribed and therefore was left under the sole control of illicit drug regulation.

At face value these moves could have closed down cannabis' career as a medical drug but, even as it was removed, cannabis was beginning its comeback as a licit medicine and concerns were raised over the illicit drug classification system. The situation that existed in 1973 was open to re-evaluation and the removal of cannabis-based medicine from the medicine cabinet was perhaps a hiatus in the plant's history. Scientific and lay knowledge around cannabis expanded from the 1960s onwards and cannabis re-appeared in different therapeutic forms for a range of uses including, as an anti-emetic, as an appetite stimulate for AIDS related wasting, as an anti-glaucoma agent, for the treatment of asthma, and for neurological disorders including epilepsy and Multiple Sclerosis (MS) as well as an analgesic. Different forms of cannabis were important at different stages. Two primary phytotherapeutic cannabinoids emerged, THC and CBD followed by synthetic cannabinoids such as nabilone. Within ten years of cannabis tinctures' removal in the UK, synthetic cannabis-based drugs entered the clinic. These drugs were little used and had numerous problems, not least their placement in the most restrictive schedules of drug control systems, and patient pressure drove demand for additional products. Cannabis, in a botanical form, appeared to offer a more effective way forward for patients who self-medicated and for a small start-up UK pharmaceutical firm which was developed specifically to look at herbal cannabis. It developed a cannabis-based medicine, Sativex, in an attempt to bring cannabis extracts back to the medical market. Expert committees and professional bodies delved into therapeutic cannabis and clinical trials were initiated to move anecdotal reports of efficacy onto an evidence-base for both synthetic and plant derived cannabis-based drugs. Emergent medical use helped to re-open debates on cannabis and drug policy.

With cannabis' twin roles being re-instated, the concept of cannabis therapeutics became tied up with drug control discussions from the 1970s onwards. Cannabis' position in the Misuse of Drugs Act had always been controversial in the UK and it appeared that the policy environment around cannabis had shifted when it was downgraded in 2004 to Class C. Sativex was licensed in Canada and provided to patients, in the UK, on a named-patient basis, circumventing the UK regulatory process and it appeared that it might shortly be made a licensed medicine in Europe. Highly controlled pharmaceutical cannabis derivatives like dronabinol were transferred to less restrictive schedules in the international and US scheduling systems to facilitate their entry into the market. In the US one previously abandoned cannabis-based drug, nabilone, was returned to the market in May 2006 by Valeant Pharmaceuticals and was licensed by the FDA as an anti-nausea drug in cancer chemotherapy management.⁴ It appeared that cannabis was moving more in-line with opium and morphine in that it could exist legitimately in both the controlled illicit drug and licit medical structures.

Re-medicalizing cannabis

The process of re-medicalization raises many questions. Why was cannabis re-considered as a medicine? To what extent was it re-medicalized and how did this process take place? What was the impact of cannabis' role as a medicine on discussions of drug policy and vice versa? Yet, while there is useful existent research on the history of cannabis and related themes such as user activism and the pharmaceutical industry, there is little research on the therapeutic use of cannabis in the UK from 1973-2004 when cannabis therapeutics developed within the context of fluid drug control policies. This thesis was framed therefore as a history of science and policy-making. It began from the hypothesis that the re-medicalization of cannabis was underway and was important for the environment in which UK policy on cannabis was constructed. Re-medicalization was defined as the introduction of medical uses and structures for the drug, as distinct from non-medical illicit usage and control structures. It recognized that full re-medicalization had not been established but rather sought to examine the intervening stages of that transition, from research, to product development, to clinical trials, and regulation. The project aimed to study the process whereby boundaries

shift between illicit ‘drug’ and licit ‘medicine’. It considered what kind of ‘borderline substance’ (the regulatory term used for tobacco) cannabis had become. To understand the process of re-medicalization the thesis aimed to analyze the trajectory of scientific research after the removal of cannabis tincture in 1973 and the interests involved, in particular, the role of scientific research and allied professions; industry; drug technology; and user activism. Within this it sought to consider the interaction of science and medicine with policy through an examination of the policy role of expert committees and the impact of re-medicalization on the policy environment. It focused primarily on the UK, although some account was taken of different national contexts. Its main focus was from 1973 when cannabis was dropped as a medicine to 2004 when cannabis was downgraded to Class C and follow-up clinical trials had been initiated and an additional submission for Sativex to the European Agency for the Evaluation of Medicinal Products was about to begin. It did, however, take account of developments just prior to 1973 which enabled research in the 1970s to take-off, as well as important developments that occurred after the main research period of the thesis but whilst research and writing-up took place. It drew inspiration from a rich supply of archival material and key informant interviews.

Defining cannabis

If the process of re-medicalizing cannabis was complex so too is the terminology used to describe what was happening during the process. The terms drug, cannabis, and even medicine can have a multitude of different meanings. Medicine and drug have often been used interchangeably but this is not always appropriate. The term drug has become increasingly linked to illicit recreational substances, whereas traditionally the term would have been applied to the active ingredient of a medicine. The use of terms such as pharmaceuticals, and therapeutics also confuse the issue.⁵ In direct relation to cannabis there are different terms in common use for the plant: cannabis; marihuana; marijuana; ganja; as well as the more common parlance of pot; weed; grass; or skunk. These terms are used generally to refer to the dried flowers, stems or leaves of female cannabis plants. I have used the UK version throughout, referring to cannabis even when discussion of American developments refers to marijuana or marihuana. Then

there are the different terms which refer to parts of cannabis usually in relation to their non-medical use such as cannabis resin or hashish, a substance produced from the resin of the flowers which produces a more potent substance than the dried leaves. The term cannabis can also cover a number of different cannabis species: *Cannabis indica* and *Cannabis sativa*. Different versions have been more popular at different times and places and have different components and activities. Hemp, for example, refers to the variant which does not contain a psychoactive element and in Europe was most widely used in rigging for ship's sails.

Cannabis can contain over sixty compounds termed cannabinoids (or since 1999 the term phytocannabinoids has been suggested) such as cannabidiol (CBD) or cannabinol (CBN) and delta-9 tetrahydrocannabinol (THC), each with different functions.

Phytocannabinoids or phytomedicines are those extracted from a plant as opposed to a synthetic chemical. Different variants and different growing conditions can lead to the production of different amounts of these constituents. Several medicines have been developed from cannabis. In the thesis for the sake of simplicity I refer to cannabis-based medicines, but this term can cover a variety of different types. From 1973, interest focused on the active psychoactive principle of cannabis, THC. This was followed by the development of synthetic rather than phytocannabinoids such as synthetic versions of THC usually administered in tablet form. The flowers, stems or leaves of cannabis were originally used as a medicine, either smoked often combined with tobacco or taken as a tea. In this instance I have used the term: herbal cannabis. Common in the nineteenth century was the use of cannabis extract, that is, extracts of cannabis in alcohol prepared by percolation, or cannabis tincture prepared by a dilution of cannabis extract. The latest form of a cannabis-based medicine, Sativex is a cannabis-based medicine extract (CBME), one that contains a mix of phytocannabinoids including CBD and CBN and is delivered in a spray form.

The Structure of the Thesis

The thesis is divided thematically and is largely chronological although some chapters overlap in time. The following section provides an explanation of how the thesis is structured and how the themes under investigation fit together.

Chapter one sets the background to the thesis and describes the methodology utilised in this project. The initial section provides an overview of the history of cannabis prior to 1973 and places the thesis within the context of the historiography of cannabis. The literature review indicates useful concepts from history and the social sciences that have been applied to this thesis. The remainder of the chapter describes the historical methodology used to build on the literature review through the use of archival, documentary, media, and interview sources.

The opening two chapters of the main body of the thesis concentrate on the trajectory of cannabis research through a study of the role of scientific knowledge, professional communities and individual scientists. The first of these, chapter two, considers the emergence of interest in cannabis research just prior to the removal of cannabis tincture's PLR in 1973. Through an analysis of archival material, the chapter focuses on a case study of the work of Sir William Paton, an influential British pharmacologist of the period. The chapter considers, through a study of his research, how awareness about cannabis was raised through increased recreational use and the subsequent need for drug control and how understandings of cannabis filtered through to discussions over cannabis' position in the developing control mechanisms. It looks at how major scientific advances, such as in medicinal chemistry and the discovery of THC, opened up new avenues for research. It explains how hindrances to research were partially overcome which allowed laboratory research on the chemistry and pharmacology of cannabis to progress and expand the fundamental understanding of cannabis. In particular, this section raises the problem of the availability and quality of the raw material for researchers. It analyses how new research placed emphasis on the harms associated with cannabis, especially potential detrimental long-term effects. Finally, it reveals early concerns around the concept of therapeutic cannabis and how this influenced debates over drug policy and the relative harms of illicit substances.

Chapter three concentrates on the initial re-interest in cannabis' therapeutic properties by British pharmacologists in the 1970s. It focuses on the development of clinical pharmacology and considers the role played by JDP Graham a pharmacologist who began to write more positively about the drug and who was influential in expert

discussions on cannabis in the 1970s. It looks at how forces of necessity in the clinic led to acceptance of cannabis as a therapeutic for the alleviation of the nausea associated with cancer chemotherapy. In particular, the chapter highlights the importance of the form of cannabis under study and its mode of administration. The chapter concludes in 1982 with the re-establishment of cannabis as a medicine through the limited approval of a single entity chemical, cannabis-based medicine in the UK and a slowdown in the development of the cannabis research field due to a failure to understand cannabis' mode of action and changing public health priorities that drew researchers away from cannabis research.

The interplay between science and policy is considered in chapter four. This chapter focuses on 1972-1982 a period that saw the development of expert advice in the illicit drugs field and this section concentrates on the role of the Advisory Council on the Misuse of Drugs at the time when Paton and Graham were carrying out their research. Through an examination of three distinct periods the chapter considers shifting attitudes in the policy environment towards the control of cannabis, the interplay between science and policy and in particular the growing role of therapeutics within discussions as well as the impact of the policy environment on the process of re-medicalization.

The following four chapters (5-8) deal with industry, user activism, the further development of expert advice and the development of clinical trials. They concentrate mainly on the period after 1997 which saw increased incentives for the re-medicalization of cannabis, though they also provide the background to these developments. These chapters overlap in time but they provide a thematic approach to pivotal events and developments from the perspective of different stakeholders.

The first of these four chapters, chapter five, takes account of the pharmaceutical industry's role in the transition of cannabis as a therapeutic from kitchen physic or self-help into the clinic and then into the marketplace. The chapter charts a progression from the initial lack of interest in cannabis by industry, to a temporary interest by the pharmaceutical industry which yielded the first licensed synthetic cannabis-based drugs and provided important materials for academic research and facilitated the breakthrough

in the understanding of cannabis' mode of action. This breakthrough provided the foundation for a more sustained interest in cannabis therapeutics in the 1990s and industry involvement increased worldwide. This chapter focuses on the involvement of a small UK biotechnology firm, GW Pharmaceuticals and places it within the context of the rise of phytopharmacy. GW Pharmaceuticals represented the realisation of a domestic pharmaceutical industry interest in cannabis. It drew inspiration from an interest in botanical substances and re-focused the spotlight towards extracts of cannabis rather than single-entity chemical substances. The impact of the form of cannabis utilized developments in technology and delivery systems, and standardization are considered.

Lay knowledge and activism underpinned some of the discourse in science, policy and industry. Chapter six traces activism, from campaigns for drug liberalisation of which therapeutic cannabis was one aspect, to the development of specific campaigns for cannabis therapeutics and in the US the development of the concept of medical necessity in relation to glaucoma, cancer and AIDS in the 1980s and early 1990s. It focuses on a case study of the role of multiple sclerosis (MS) patient associations in the UK which campaigned for research and access to cannabis in the 1990s and considers their impact on the scientific, clinical, industrial, and policy spheres.

Chapter seven takes the story of expert advice and the relationship between science and policy forward to consider the role of professional bodies and expert advice in the period 1997-2004. It traces the expert discussions through the release of pivotal reports that emerged from the BMA and the House of Lords in the late 1990s and discussions over the scheduling of cannabis in the Misuse of Drugs Act after the turn of millennium. Through an examination of these expert discussions the chapter explores the impact of developments in the medical use of cannabis on the policy environment and their impact on the debates upon the process of re-medicalization itself.

'Evidence', clinical trials and regulation are the subject of chapter eight. After the expert discussion of the 1990s, the government agreed to permit the licensing of

cannabis-based medicines if successful in clinical trials. This chapter charts the initiation and development of the clinical trials, and their outcomes. It looks at the issue of 'evidence' and the problems that clinical trials posed for cannabis and the issues around regulation of cannabis-based medicines. The chapter concludes at the point at which Sativex, a CBME, was in the process of passing through the medical drug licensing system and as a new series of clinical trials were due to commence.

Chapter nine, the conclusion, draws together these various interlocking themes providing an overview of the process of the re-medicalization of cannabis and links the history to a few important developments that took place just after the main research period of this project. Cannabis was viewed as a 'peculiar' or 'borderline substance', one whose position as a medical and or recreational product was fluid and dependent on a myriad of developing and competing factors. In addition to a story of a plant, an illicit drug and medicine it is also the story of developing disciplines, national interests, commercial interests, patient perspectives, and 'evidence'. Uncertainty has been crucial in the story of the process of re-medicalization and where therapeutic cannabis will go from the point at which this study ends is uncertain but this thesis provides a window into an ongoing process. Emergent cannabis-based medicines appeared to be able to exist within the drug control systems, and questions shifted to the broader picture of the relative positions in terms of harm of both illicit and licit drugs and to the entire framework of control.

¹ G. Edwards, and J. Strange, 'Britains Drug Crisis,' *the Independent*, Thursday, 3 March 1994: <http://www.independent.co.uk/news/uk/britains-drugs-crisis-recipe-for-dangerous-medicine-viewpoint-1426619.html>

² See appendix 3.

³ See appendix 5.

⁴ See appendix 6.

⁵ See A. Anderson, *Makings Medicines* (London: Pharmaceutical Press, 2005), p. 4-5.

Chapter One

Historiography

‘Cannabis spray beats MS spasms’ Daily Mail, March 13th 2007.

Each of these five simple words headlined in a newspaper article in 2007 carries a heavy load of baggage and such succinct headlines that have emerged in recent years mask a very complicated history. Cannabis-based medicine ceased to be licit medicine in 1973 in the UK, so why did it appear to be re-starting a successful career as a medicine? Furthermore, cannabis is more noted for its administration through smoking so how and why did a new delivery method emerge? Cannabis has been perceived as having applications for many complaints, so why was it used to treat MS and to what extent did it beat MS spasms? This raises further questions such as the extent to which cannabis has been re-medicalized, how has this process taken place and how has it been incorporated within the drugs policy environment? The thesis is framed as a history of science and policy-making and has employed standard contemporary historical methodology. The subject of history itself has undergone development and has moved beyond narrative to analytical approaches and from a passive subject to taking greater role in contemporary debate. This has been highlighted in recent years as the application of an historical approach has become increasingly important in the public health field. This chapter highlights useful approaches and lacuna in the existent literature around cannabis, public health and drug control. It concludes with a description of the methodology utilised for this study.

Literature Review

In turning to existent literature for explanations of the process of re-medicalization even a cursory scan of most libraries or bookshops will reveal a range of books on cannabis: from how to grow it; to popular histories of its medical and recreational uses; scientific tomes on its pharmacology and the legalization/prohibition debate.

The angles of interest to writers on cannabis have also undergone development over time. A literature review revealed useful approaches and interesting questions that had already been utilized in the historical study of cannabis and established where further research could contribute to the historical understanding of cannabis. Social science literature on cannabis and related themes also provided useful methodologies to apply to this study. Catalogue and database searches included: the Wellcome Library, British Library, Senate House, University of London, Pubmed; Historical Abstracts, and JSTOR. Further material was garnered from bibliographies and PhD databases and by word of mouth. Search terms incorporated the myriad of words related directly to cannabis but also relevant topics such as expert advice and the pharmaceutical industry. Search terms were kept under review throughout the research process.¹ The initial search was wide ranging and encompassed all time periods and captured texts on both the UK and international context. Finding more than enough material for a UK based study, international comparisons such as with the US and Australia were scaled back and remain a potential area for future work. Material was stored in an Endnote database.

A variety of approaches to the study of cannabis emerged from the literature review as did useful methodologies from related themes which had not been applied to the historical study of cannabis. These have been categorized into eleven topics within which salient themes for this thesis are discussed.

Popular histories of cannabis

When popular, policy and scientific interest in cannabis re-emerged in the 1960s numerous popular histories of cannabis emerged to provide brief overviews of its history, and or detailed explanations of the techniques for using cannabis recreationally.² ‘Cannabis culture’ emerged through popular texts and many focused on the legalization/prohibition axis of the debate. David Solomon edited a collection of essays in 1969 on the historical, sociological, and cultural aspects of cannabis, in which he argued for the legalization of cannabis.³ However popular histories tended to be US-centric and focused on the role of cannabis as a recreational drug. They provide a start point but

are perhaps more useful as a primary source for attitudes towards cannabis. They do indicate however that medical use of cannabis needs to be studied in the context of the prohibition and legalization debates.

Cannabis from ancient times.

Academic historical interest focused initially on the long-term history of cannabis and sought to bring an historical perspective to contemporary drug problems. Interest in the 1970s focused on the ancient use of cannabis or its long history of use throughout the world.⁴ Theodore Brunner, for example, analysed the literary evidence for cannabis use in ancient Greece and in Rome, and contributed an in-depth analysis of the evidence for specific incidences of cannabis use in specific ancient populations.⁵ Historical use of cannabis was co-opted sometimes to support contemporary arguments for and against the use of cannabis.⁶ The presumed relationship between cannabis, violence and crime pushed by Henry Anslinger, Head of the Federal Narcotics Control Board (INCB) in the US was given support by the supposed use of cannabis by the Assassins, a sect of Shia Muslims, who were alleged to have taken cannabis prior to assassination attempts. Casto challenged the view that history could be used in such a manner to support policy and he attempted to debunk the Assassin's tale as myth.⁷ More recent material by Berridge has also considered the relationship between history and policy and challenged the assumption of Queen Victoria's use of cannabis for dysmenorrhoea and its utilization in policy debate.⁸

Other academic writing in the 1970s and early 1980s traced the long history of cannabis from ancient times to the modern day.⁹ One feature of the medical history of cannabis has been the publication of histories by the scientists involved in the re-investigation of cannabis. In the US, Mikuriya, a former director of marihuana research for the National Institute of Mental Health (NIMH) and consultant to the National Commission of Marihuana and Drug Abuse, wrote in the mid-1970s of the amnesia suffered around cannabis' original uses.¹⁰ The re-investigation of old literature in the light of contemporary knowledge and the similarities between contemporary and historical concerns over issues such as toxicity, delivery methods, and dosage has been a

another facet of historical research.¹¹ That cannabis was not always viewed as an illicit dangerous substance but was initially prized as a food, fibre and medicine was shown by Ernst Abel.¹² Abel described how Emperor Shen Nung (2700BC) was credited with the discovery of cannabis' therapeutic uses. The world's oldest pharmacopoeia dating from the first or second century AD – *Shen-nng pen ts'ao ching*, based on the work of Shen Nung - recognised the psychoactive properties of cannabis and later editions recommended that cannabis be used for treating gout, malaria, and rheumatism. Hua To, founder of Chinese surgery, was said to have used cannabis mixed with wine to anaesthetise patients. In Europe, hemp, the non-psychoactive variant of cannabis, had been cultivated since Roman times, but little was known about cannabis' medical uses, though Galen, the second century Roman physician, wrote of its use in the elimination of intestinal gas and as an analgesic. From the sixteenth century hemp was widely cultivated to supply fibre for textiles and for ships' rigging and sails. Due to the European growing conditions little was known about cannabis' psychoactive properties until cannabis was introduced from the East in the nineteenth century. Abel went on to trace the interweaving of cannabis into the development of prohibitive legislation in the twentieth century. Such histories demonstrate how perspectives on substances fluctuate. Perhaps the attempt to frame cannabis exclusively as an illicit substance is a brief departure from the norm rather than a defining feature of its history. This thesis aims therefore to give an idea of greater complexity around cannabis rather than the more dominant preconception of cannabis as an illicit substance. These texts require updating to take into account developments after the 1980s and to provide a history focused on the medical aspects of the debate. Utilizing such contemporary history allows also the use of contemporary historical methodology, such as oral history techniques, for the supplementation of documentary sources.

Cannabis in the UK. From 'wonder drug' to sidelined substance

The nineteenth century European use of cannabis has been of particular interest to historians.¹³ Lewis highlighted how debates and fears raised in the 1960s over drugs such as cannabis and heroin bore striking similarities to those generated in the nineteenth century.¹⁴ Historians' interest fell on the use of cannabis by literary figures.

for instance, Dumas. International comparisons of the recreational use of cannabis have been made.¹⁵ Medical use was also of interest and Berridge in the 1980s described the introduction of cannabis to the UK as a therapeutic.¹⁶ It was introduced from India in the 1840s by William O'Shaughnessy, an Irish doctor, who served as Professor of Chemistry and Medicine in the Medical College in Calcutta. In studying the Indian use of cannabis he wrote on its analgesic and sedative properties, and he found major success in treating muscle spasm caused by tetanus and rabies and with vomiting from cholera. His work attracted considerable attention as these diseases were much feared at the time. This 'medical necessity' was an important incentive for cannabis therapeutics post- 1973 such as in the case of HIV/AIDS. Commercial success for cannabis was achieved when O'Shaughnessy gave *cannabis indica* to the pharmacist Peter Squire who produced an extract, Squire's Extract that became readily available for many ailments. Official recognition was achieved and quality standards set when cannabis-based medicines were included in UK and US pharmacopeias in the 1850s.¹⁷ By the nineteenth century the medicinal value of a plant was linked to its 'active principle' rather than the use of the plant itself and a major trend in chemistry in the nineteenth century was the quest for active natural products.¹⁸ Numerous alkaloids were isolated in pure form plants, for instance, morphine from the poppy was purified and used for medicine. Such alkaloids were relatively easy to isolate, but the cannabinoids, forms of terpenoids, from cannabis proved more difficult.¹⁹ Cannabis' value as a medicine increased in the 1890's when a group of chemists Wood, Spivey and Easterfield at Cambridge University succeeded in obtaining a relatively pure extraction of a terpene and which was thought to be the active principle of cannabis which they called cannabinal.²⁰ This discovery facilitated further research and articles appeared on its use as an antibiotic, appetite stimulant and antidepressant, and for opium addiction. Smoking was recommended as the fastest and most effective method of delivery.

At this stage, it was generally regarded as a safe medicine. Pre-empting controversial contemporary comparisons with other drugs, Walter Ernest Dixon, a leading member of the Rolleston Committee on Morphine and Heroin Addiction in the 1920s and an opponent of the penal narcotic policy of the American model, placed cannabis in the same category as tea and coffee rather than with drugs like heroin.

Cannabis-based medicines such as cannabis tincture were available as over-the-counter products and cannabis extracts were found in many proprietary medicines. It was often combined with opium and capsicum extracts as a pain killer.²¹ Histories of the introduction of cannabis as a medicine therefore raise important concepts for a study of its re-medicalization post-1973. The thesis considered if the diseases cannabis was used to treat were important to its survival as a medicine. Who produced cannabis-based drugs and how were they supplied? How were safety and quality standards set? In what form was cannabis used and how was it delivered? Discussion of the safety of cannabis raised questions as to the perception of cannabis' harm relative to other drugs such as heroin and to widely used licit substances like tea, coffee and alcohol.

Historical research in the 1980s also demonstrated that cannabis as a medicine was limited and medical usage had declined rapidly by the end of the nineteenth century. Berridge offered explanations for its limited use, namely problems with its uncertainty of action, irregular supply, and its inability to compete with opium products in terms of availability and mode of delivery.²² The pure active principle had not been isolated, a major problem at a time when the pharmaceutical sector was developing around the production of single chemical entities. Its chemical structure meant it was not water soluble, unlike a major competitor, morphine. This meant cannabis could not be administered via new drug delivery systems such as the hypodermic syringe which was rapidly gaining currency. Issues of standardization posed further complications. In the nineteenth century and for most of the twentieth the plant could not be standardized and therefore a standardized medical product could not be produced. There was no standard for either the total content of cannabinoids or the proportions of individual cannabinoids, leaving the product in a weakened position compared to emergent synthetic single entity chemicals such as aspirin. All these factors limited its utility as a therapeutic in a marketplace increasingly controlled by the developing pharmaceutical industry. Therefore the thesis considered if overcoming these problems allowed the process of re-medicalization to take off.

Histories of nineteenth century use highlighted another key issue around cannabis, that of the psychoactive impact of the plant and the fear that this posed for the safety of

individuals and society. Cannabis became linked to mental health problems, especially insanity, and crime. Much of the evidence for this came from India where it was feared that hospitals were full of patients with mental health problems allegedly caused by cannabis use. A major inquiry, the Indian Hemp Drugs Commission of the 1890s examined the trade in hemp drugs and whether cannabis use should be prohibited. The commission came out against a link between cannabis and crime, and any need for prohibition. The link between cannabis and mental health is as hotly debated today, as it was in the nineteenth century, and the conundrum over cannabis' role both in the treatment and cause of insanity has occupied historians.²³ Though the commission's report was largely ignored at the time in the UK, it became of interest to historians and scientists from the 1970s onwards, particularly in relation to the link with insanity.²⁴ Kalant reviewed the report and reflected on its relevance to contemporary problems.²⁵ Interest in the mental health aspects re-emerged from 2000 onwards as debates over the alleged link were revived most notably by British psychiatrists. Basu wrote on the alleged evidence from the Hemp Drugs Commission for the link to insanity.²⁶ Mills worked on the growth of lunatic asylums in India in the nineteenth century, and placed cannabis within the colonial discussions of madness and the impact of these discussions upon the UK discourse.²⁷ A clearer picture is required of the impact of this controversy on drug policy at both the national and the international level and how it acted as a countervailing force to re-medicalization. Existent historical reviews tended to be confined to a brief description within more general histories of other drugs or within social histories of cannabis. Further work was required to look at cannabis specifically; in relation to the latter half of the twentieth and early twenty-first century; and with a focus on medical rather than recreational use.

Cannabis and American drug control policy in the twentieth century

One of the more contentious facets of the historiography is the discussion surrounding the development of prohibitive drug legislation, especially in the US. Increased use of cannabis in that country during the 1960s, and especially after the Vietnam war, led to an increased interest in the history of the rationale behind the prohibitive policies. Policy history flourished in the 1970s and 1980s but was primarily focused on events

in the US and centred on the 1930s when early prohibitive policies were implemented. The US enacted its own legislation via the Marijuana (Cannabis) Tax Act (MTA) of 1937 against cannabis through the Federal Bureau of Narcotics headed by Harry Anslinger. Historical debates revolved around the reasons behind the establishment of the MTA. Arguments ranged over the relative importance of anti-Mexican sentiment, the link to crime and insanity, and role of the individual in the shape of Anslinger, and the Federal Bureau of Narcotics. Musto in a review of the MTA argued for a greater synthesis in understanding.²⁸ Himmelstein queried the argument that the MTA was due to anti-Mexican sentiment or the moralistic policies of Anslinger and raised the question of the ideology surrounding the drug and drug control.²⁹ Alternatively, Saper suggested that American narcotic laws had developed more through accident, and the acceptance of drug myths, rather than through rational decision-making.³⁰ Bonnie and Whitebread brought a legal perspective to the history of cannabis, with the use of historical documents surrounding the cannabis laws and the public policy response.³¹ They sought cannabis law reform and moved the emphasis from public safety to public health and in the process they elucidated why contemporary laws were established. Their book provided an early example of a comprehensive history of cannabis prohibition in the US. It highlighted the construction of cannabis as a 'monster'; the 'politics of fact finding'; the establishment of the Marijuana Tax Act; the stepping stone theory: the idea that cannabis use led on the use of 'harder' drugs; the escalation of punitive responses to cannabis use in the post-war period; and the creation of the United Nations Single Convention on Narcotic Drugs of 1961. This legal history has been developed with further texts such as Erlen's review of the Federal drug control system from the 1870s to 2000 via a study of Supreme Court cases. He revealed the gradual increase in power accorded to the criminal justice system.³² The incorporation of cannabis within criminal justice is an important aspect within discussion of the process of re-medicalization. These works provide one slice of policy history at defining moments in American history in relation to cannabis. They provide useful themes to consider such as the competing interests involved in the formulation of policy, and the hindrances to rational decision making. The re-medicalization of cannabis took place within the context of fluctuating drug policy both internationally and in the UK yet an in-depth policy discussion that is UK centric is lacking.

Cannabis and international agencies and policy

The rise of international organisations and associated drug control policies of which cannabis has been a part since the 1920s is an important contextual basis for understanding the process of re-medicalization, since for most of the twentieth century cannabis has been viewed as an illicit drug. Cannabis' medical utility was eroded in stages, through the development of mechanisms of control, and cannabis became reframed as an illicit rather than medical substance. Since 2000 historians of public health have argued for further research on the globalization of the governance of health and the treatment of illicit drugs.³³ Berridge has highlighted the importance of understanding this historical context. Recent research, such as by Mills, has expanded our knowledge of colonial production and supply and the development of initial prohibitive international and domestic legislation. He demonstrated how the politics of Empire led to the prohibitive drug policies and scientific evaluation was pushed to the sidelines in contrast to the demands of supply and trade.³⁴ He revealed the battle between the producer and the trader and how producers sought to avoid tax imposed by the British Administration which led to cannabis becoming associated with crime by the British Government. In domestic policy he demonstrated how 'policy seems to have been driven by mistakes and misunderstanding rather than well-informed debate.'³⁵ Kendell's work provided a discussion of the development of initial international regulation and demonstrated how cannabis became caught up in international drugs control.³⁶ Through such work historians indicated how, in the early twentieth century, multi-lateral agreements had developed around narcotic drugs and replaced the earlier bi-lateral agreements such as existed between Britain and China and were largely concerned with issue of trade and supply. The 1912 International Opium Convention (Hague) laid the foundation of international drug control systems. Cannabis was not included in that Convention though Italy, South Africa and the US applied pressure for it to be considered. The Convention led to the introduction of regulations in Britain around 'dangerous drugs' with the Dangerous Drugs Act of 1920. In 1925 the Geneva Convention marked the start of a sustained focus on drug control. Essentially focused on opium, cannabis was included under pressure from South Africa and Egypt and this impacted on the manufacture, sale and movement of crude cannabis ie cannabis resin

for purposes other than medical or scientific purposes.³⁷ The Convention was relatively weak and cannabis, for example, could still be shipped through non-signatory countries. Britain, as a signatory, introduced the Dangerous Drugs Act of 1928 which banned recreational use of cannabis. With little use of cannabis in the UK at this time there was little opposition to these moves. Cannabis as a medicine was unaffected and cannabis tinctures, for example, were still available.³⁸

Much historical work on the development of prohibitive drug policy is on pre-Second World War developments although Bruun looked at the Nordic experience of control of medicines and at international drug control after the Second World War.³⁹ The influence of the US on global drugs control after the Second World War has been studied, in particular, the development of two United Nations Conventions: the 1961 Single Convention on Narcotic Substances and the follow-up 1971 Convention on Psychotropic Substances.⁴⁰ The impact of the US on the evolution of drugs control has been considered by Bewley-Taylor. He discussed the initial development of international control up to the Second World War, to the export of US drug control policies with US pressure for the Single Convention in the post-war period. He highlighted the impact of the US on the UN and argued that US influence was possible due to its hegemonic superiority in the post-war period. He demonstrated the US dissatisfaction with the alleged weakness and functioning of the global drugs regime post-1961. He went on to suggest that drug control policy was largely ineffective and led to the destructive 'war on drugs' approach. The framing of regulatory frameworks has been analysed by McAllister. He provided an historical account of the development of global drug control regimes and considered the involvement in policy formation of various interests: colonial concerns; pharmaceutical interests; and the role of interpersonal relationships. Of particular interest for this study is his discussion of the development in the West of a split between licit medical use and illicit recreational use, a divide that cannabis appeared to straddle. Of relevance too was the growing perception that society had a responsibility to intervene to prevent illicit-non medical use or the abuse of drugs, an intervention which led to increased illicit manufacture and trade.⁴¹ This division between medical and recreational use requires consideration in the context of the re-medicalization of cannabis. So too does the discussion between a

precautionary and paternalistic approach and liberal principles. McAllister highlighted the role of the pharmaceutical industry as an interest group important in the formation of drug control policy and demonstrated how the 1961 Convention favoured a medical–industrial complex and focused on control of raw material affecting the producer rather than the control of new synthetic derivatives, an exclusion which largely continued in the 1971 Convention.⁴² This leads to important questions; what is the impact of cannabis being a plant-based medicine? What is the importance of the placement of cannabis and its derivatives within the scheduling system? What impact has this had on the development of cannabis-based extracts? Finally, the impact of international control on contemporary concerns including: patient and health care advocacy; the renewed interest in herbs and alternative medicine; harm reduction policies and the environmental and natural foods movements have been considered by Mead. She also notes how the conventions were open to interpretation, a factor important for the treatment of medical use of cannabis in signatory countries such as the UK.⁴³

There is limited work on setting these developments into the institutional context in which these conventions were designed. Histories exist of the initial developments of the international agencies such as the Red Cross. Weindling's edited collection of essays on international health organizations charted the inter-war development of the international agencies such as the League of Nations. The work highlighted tensions between national interests, ideals, class, and *realpolitik*.⁴⁴ There are some histories of the World Health Organisation (WHO) focused on the initial attempt to establish a scientific basis for the cause of poverty and disease and the role of outside expertise, but a definitive history has not been produced nor is there a comprehensive history of the drug agencies such as the INCB.⁴⁵ This leaves unanswered questions such as what response did each of these organisations take to the medical use of cannabis? Did attitudes change over time and how did they interact?

UK policy and the role of expert advice

Various responses to the international conventions were introduced by the different parties. In the UK the framing of cannabis and its derivatives in drug policy has

been reviewed by governmental expert bodies. These have included the closed in-house discussions of the Advisory Council on the Misuse of Drugs (ACMD), and the more public discussions that emerged in 1990s through the House of Lords Science and Technology Committee and professional bodies such as the British Medical Association (BMA), all of which published influential reports on the medical use of cannabis.⁴⁶ However, the role of professional bodies and expert committees has been relatively little studied in relation to cannabis despite their crucial importance in the cannabis story and rich archival material. In the UK, after the publication and initial government dismissal of the Wootton Report in 1969, Abrams, a founding member of the cannabis activist group, SOMA, considered the development of cannabis policy in the UK.⁴⁷ Popular histories have touched on the developments of national UK policy history in the latter part of the twentieth century, but the focus of historians has been the development of policy in the nineteenth and early twentieth centuries. Mills, for example, in *Cannabis Britannica* considered the initial development of British policy on cannabis up to 1928 and demonstrated how cannabis was caught up in policy on medical and intoxicant substances through political and moral agendas rather than through ‘evidenced-based policy’ and that the foundation of policy was frequently based on incorrect assumptions.⁴⁸ Hall has considered the public policy debate and the relationship between health policy, public health and the law in Australia, the UK and US.⁴⁹ Historical and social science work from the broader literature provides methods of looking at the role of expert advice which can be applied to the cannabis field. The term expert advice covers a variety of structures, as Barker and Peters have described, ranging from, from institutional expert civil servants, advisory committees, to more informal information networks and contacts.⁵⁰ In the UK context, MacLeod has shown how the role of the professional and the expert developed in the mid Victorian period while Hamlin has described how disputes flared between these experts.⁵¹ Expert advice evolved into a more formalized setting in the twentieth century and Berridge in her analysis of smoking policy in Britain has discussed the development of advisory bodies or expert committees.⁵² She placed deliberations over smoking in the context of developing relationships between experts and the state, and the growing demand for the ‘rational expertise-based model’ within government, especially within the context of health policy and developments in the NHS. As Berridge has shown the model of

channelling scientific advice into policy was utilized in the illicit drugs field, and the formula was developed in detail during the 1970s, with the formation of the Advisory Council on the Misuse of Drugs.⁵³ As will be discussed, it was during the 1960s that we see some of the initial expert committees established in the illicit drugs field, on an ad hoc basis, and in the 1970s the formation of statutory committees which became deeply concerned with the cannabis question. The formal structure of an expert committee may be seen as one of the better ways of achieving evidence-based policy. For instance, Bulmer has shown how it provides a method of neutralizing a subject by taking it out of the political arena.⁵⁴ This is especially important with a highly divisive issue such as cannabis. How far a committee can be successful in this is open to question.

One important theme that emerges from the literature is the role of uncertainty. Jasanoff, for example, in looking at the role of expert committees in the US, in relation to carcinogens in the 1970s and 1980s, has shown their growing importance to policy-makers, and she illustrates how the technocratic model is by no means value-free.⁵⁵ Her work considers what lies behind the construction of 'evidence' or expert advice, and the *'trade off between risks to health/environment and the economic/social costs of regulating.'*⁵⁶ Jasanoff demonstrated how *'scientific uncertainty is a resource that can be mobilized by regulators...in effect to influence policy.'*⁵⁷ This is particularly interesting in the case of cannabis, where uncertainty over its medical benefits and potential hazards, were utilized by those on both sides of the debate. Hilgartner in a review of expert advice, in relation to diet and cancer, demonstrated how uncertainty could be invoked to justify action or inaction.⁵⁸ Hilgartner raises another issue, that of the role of private/public discussions. Hilgartner likened the work of expert advice to the world of the theatre with the performance or report/publication on view at the front of the stage, whilst backstage the actors, or in this case the experts, could discuss and rehearse their 'performance' in a private enclosed space. Leaks blurring the division between this public and private space are viewed by Hilgartner as a breakdown in stage management. This approach is useful in the case of cannabis where uncertainty, conflict, and leaks played key roles in the expert discussion of the 1970s. Florin, in a review of the relationship between science and policy in relation to coronary heart disease prevention, aimed to assess the extent to which policy on health promotion in general practice

was based on evidence.⁵⁹ She indicated that high levels of scientific uncertainty led to different interpretations of the evidence by those from different backgrounds. This was a problem in areas that lacked an independent system such as an expert committee. The literature raised relevant questions for a study of cannabis: did uncertainty over cannabis' effects also impact within the framework of expert committees and what impact did it have on advice and its uptake? What impact did domestic drug policy have on re-medicalization and did re-medicalization have an impact on discussion on cannabis more generally? How were expert committees and enquiries set up and how did they relate both to the changing views of cannabis and to the roles of the organizations concerned?

The re-medicalization of cannabis

Historical work on the medical use of cannabis has expanded since the late 1990s. Mathre provided an edited collection on the therapeutic use of cannabis in which she questioned the polemic division of 'good' and 'bad' drugs as a useful premise.⁶⁰ In the same volume, Aldrich, a cannabis historian, contributed an account of the therapeutic use of cannabis from ancient times through to the 1990s. One section in particular provided a helpful narrative and brief analysis of the re-interest in medical marijuana in the US, after the 1970s.⁶¹ With a focus on scientific discoveries, and the role of user activists, namely AIDS patients, he concluded that science, in the case of cannabis, had not been linked to policy. The different treatment of cannabis derivatives and the crude-plant product emerged as an important consideration. Aldrich's work raised interesting questions over the medical history of cannabis: who makes decisions over that which is considered to be a useful drug – politicians, lawyers or scientists and what influences that decision?

By the turn of millennium additional popular histories emerged, this time with a greater focus on medical use. The Emperor Wears No Clothes pressured for the right to smoke cannabis and questioned the science over the issue of brain damage allegedly caused by cannabis use.⁶² It advanced the theory that cannabis policy in the form of the Marihuana Tax Act was related to industrial interests protecting their trade.

The wine writer Patrick Mathews reported on the 'cannabis culture' in England and revealed some of the pressure provided by user activists for access to cannabis. He offered an interesting, popular account of the role of industry in the moves towards re-medicalization of cannabis through interviews with the founder of GW Pharmaceuticals, a company licensed in the UK to grow cannabis and carry out research into cannabis-based medicines.⁶³ Booth's *Cannabis: A History*, though focused on the US, offered some UK comparisons and provided a useful narrative chapter on the re-interest in cannabis as a medical product after 1960. He raised the dilemmas faced by doctors when weighing up the benefits and risks of the medical use of cannabis, the results of clinical trials, the problems of synthetic cannabinoids and the role of user activists.⁶⁴ One of the few popular books dealing specifically with the medical use of cannabis is that by Alan Bock, editorial writer for the Orange County Register. He delivered a journalistic-style review of American politics surrounding medical cannabis and, in particular, the implementation of Proposition 215 which allowed for compassionate access to cannabis.⁶⁵ These popular histories offer an interesting start point but are primarily anecdotal, brief introductions to the field. Issues such as the role of industry and user activism raised by these texts would benefit from a more in-depth archival and oral history approach to ascertain how they impacted on the process of re-medicalization. Documentary histories have also appeared publishing key primary texts from the nineteenth and twentieth centuries on a range of issues, including the development of prohibitive policy, to campaigns for medical access to cannabis. Musto's documentary history focused on aspects of drugs in America.⁶⁶ Belenko's collection, focused on three key themes; that of periodic concentration on specific drugs; tensions between medical or punitive approaches to drug use; and shifts in policy attributable to politics rather than science.⁶⁷ These documentary collections provide access to useful documents but provide little by way of analysis and the texts published are obviously selective and without their broader historical context.

Additional literature emerged reviewing major developments in the science around cannabis since the 1960s, in particular, the production of synthetic drugs such as Marinol and the endogenous cannabinoids and receptor sites.⁶⁸ Reviews have emerged on the development of certain aspects of scientific discussions surrounding cannabis,

such as the controversial stepping-stone and gateway theories, which gained currency in the 1950s. The gateway theory implied that there was a sequence of drug use and that cannabis led to the use of other 'harder' hallucinogenic drugs and the theory was often used in policy discussions to justify strict controls and penalties on cannabis use. Historical reviews of these theories, such as that by John Witton and Sarah Mars, have clarified some of the debates around cannabis' impact and have also been used to inform contemporary policy.⁶⁹ A better understanding of the role of and trajectory of scientific knowledge is necessary to understand the process of re-medicalization, the fluctuating perceptions of cannabis and resultant policy.

Russo, senior medical advisor to GW Pharmaceuticals, provided a short history of cannabis' medical role, in the book *The Medicinal Use of Cannabis and Cannabinoids*, edited by Dr Guy, Director of GW Pharmaceuticals. Russo's chapter imparted a perspective on the problems of research into plants and the negative impacts of legislation upon research.⁷⁰ Histories, written by scientists involved in research and/or with industry, may provide useful insights into the problems of scientific and industrial research and production, but may also lead to questions of bias and objectivity. In the twentieth century, the history of therapeutics is inseparable from the rise of the pharmaceutical industry. Since the 1990s, industry has become an important location for research into new cannabis products. Historical literature, however, on the role of industry in the re-medicalization of cannabis in the twentieth century, especially in the UK context, is limited. That which does exist focuses on the development of synthetic products, such as nabilone in the USA, rather than the development of the herbal product, which has been the focus of UK industry.⁷¹ There is limited independent historical discussion of the role of industry in this field and the techniques for studying industry raised by existing literature need to be applied and developed in relation to the re-medicalization of cannabis.

There is a range of historical and sociological literature which provides conceptual modules for understanding the role of the pharmaceutical industry in the twentieth century. A number of studies have looked at the long history of therapeutics, highlighting the brevity of synthetic drug usage, as opposed to a long, herbal tradition.⁷² The influence of factors, such as regulatory processes and scientific advances in drug

development, has attracted attention.⁷³ Pickstone traced the growing intersection of industrial and scientific interest in the interwar years, whilst others focused on developments in the pharmaceutical industry in the immediate post-war years, a time of great optimism surrounding the advent of new drug treatments.⁷⁴ The changing focus from infectious to chronic disease and the relationship with industry has attracted attention, as have research flows between countries and the impact on industry.⁷⁵ In the initial development of the pharmaceutical industry historians cite the importance of a greater understanding of vegetable and mineral substances used as medicine.⁷⁶ In this, the isolation of an active principle was important. Major discoveries included the isolation of morphine from opium, aspirin from willow bark, and later quinine from cinchona. Authors writing about the pharmaceutical industry and pharmacy have highlighted the importance of accessibility to research material and how it can shape social and cognitive developments.⁷⁷ Histories of pharmacy and the pharmaceutical industry divide its development into between three and five stages: kitchen physic; the rise of commercial remedies; development of pathology and microbiology; growth of multinational pharmaceutical companies, acquisitions and mergers and the elimination of small-scale industry; and the emergence of small biotechnology companies.⁷⁸ The emergence of small biotechnology companies, such as GW Pharmaceuticals, provided the opportunity to exploit the gaps left unexplored by 'big pharma.' A study of the effect of small biotechnology firms, with a focus on GW Pharmaceuticals, provides an ideal case study of industry/science/policy relationships. Although histories have emerged from those involved in the pharmaceutical field, there is limited discussion of its role in the cannabis field. Furthermore, available historical literature introduces, but does not fully answer, questions as to the importance of supply, the controversy over synthetics versus plant products, and synergism (the combined effect of two or more components of a plant) versus the use of isolated single active principles. This thesis therefore considers the impact of an initial lack of industry interest, followed by its involvement from the late 1970s and the emergence of biotechnology firms from the 1990s. Within this context, it considers the impact of changing drug technology and if the ability to produce oral cannabis medicines was important as a delineator of medical/non-medical boundaries. Other issues include, what role have synthetic products, such as nabilone, and extracts of cannabis such as Sativex played in the transition and what has been the impact of an interest in the 'botanical route'?

The rise of specific disciplines: psychopharmacology and phytomedicine

A review of the literature reveals that there are deficiencies in taking account of the rise of specific disciplines, in particular, psychopharmacology (the branch of pharmacology that deals with the study of the actions, effects, and development of psychoactive drugs) and phytomedicine, (the study of plants for medical applications). Cannabis, while often viewed solely as an illicit drug, needs to be viewed as a plant and the revival of interest in its use as a therapeutic, needs to be considered within the context of the revival of interest in plant-based medicine.⁷⁹ Historical research on medicinal plants has concentrated on three aspects. First, there are the histories of the disciplines of botany and herbalism. Works centre on the early history of botany and herbals, particularly, in the Middle Ages.⁸⁰ Those who have looked at ‘medical history from below’ have stressed the nineteenth-century popular interest in medical botany and subsequent commercial development.⁸¹ Second, a more recent trend has been the study of the development of ethnobotany, that is, the study of medicinal plants and indigenous knowledge.⁸² Third, there are the histories of individual plants.⁸³ The discovery of *Artemisia annua* (*A. annua*) inspired a few thought-provoking, short pieces of historical writing including Dobson’s examination of quinine and Artemisinin.⁸⁴ Some writers stress the role of competing interests. Power’s study of drug resistance looked briefly at the history of *A. annua*’s discovery and use, viewing the acceptance of both in terms of ‘contested knowledge.’⁸⁵ Goodman and Walsh’s study of Taxol traced the ‘cultural biography’ through which a plant became a commercial product.⁸⁶ Therefore what issues associated with cannabis are related, not to its framework as an illicit drug, but as a plant-based medicine? Historians have traced the development of pharmacy and pharmacology. In terms of the development of psychopharmacology, a witness seminar on *Drugs in Psychiatric Practice* organised by the Wellcome Trust in 1998 and Healy’s book *The Creation of Psychopharmacology* traced the development of psychopharmacology and in particular looked at the role of industry, the rise of the ‘magic bullet’ approach, the importance of standardization, and the tensions between disciplines.⁸⁷ The rise of these disciplines is important for understanding the process of the development of drugs from a plant. Russo argued that Europeans were important

for the development of cannabis-based drugs as although the National Institutes of Drug Abuse (NIDA) provided the majority of funding into cannabis and introduced cannabis-based medicine, Europeans had not '*strayed quite so far from the realm of materia medica*'.⁸⁸ Many of the debates raised over plant medicine are transferable to an investigation of cannabis and allow the medical use of cannabis to be placed in the broader context of the development of phytopharmacy.

Lay knowledge, advocacy, and user activism

Lay knowledge and the role of user activists have been important for the re-medicalization of cannabis. There is considerable historical literature on the self-help and mutual aid societies that flourished in the nineteenth century and the post-war period is seen as a new period of self-help. Health activism in the post-war period has been studied and focus has fallen upon the role of AIDS activism.⁸⁹ This has been in the context of the rise of interest in the growth of single issue activism, and a small number of studies relate to activism in relation to cancer, animal rights, the environment, anti-nuclear movements, and, within this, the growing importance of internet-based activism.⁹⁰ The growth of grass-roots knowledge and the relationship between lay activists and professional groups has been of particular interest to sociologists and historians.⁹¹ Institutional history has been helpful in providing insights into this arena. Mold, for example, has reviewed the history of the drug voluntary organisation, Release.⁹² Texts, however, often review how activism led towards stricter control over drugs such as tobacco. This thesis looks at the reverse: the role of activism in attempts to regain access to drugs like cannabis for medical purposes, recreational use and to attenuate control systems.

In relation to cannabis, popular histories have explored the role of popular pressure and cannabis cultures. In relation to medical cannabis use there are a number of accounts by individual activists of their experiences. Steve Abrams, a cannabis activist and founding member of SOMA, has written on the development of SOMA and the impact of reports such as that of the Wootton inquiry and subsequent media responses upon activist groups.⁹³ Randall provides an account of his legal

battle to use cannabis for the treatment of his glaucoma.⁹⁴ In the UK, lay activists have been important in pressuring for further research, access to cannabis, and have collaborated with members of the medical profession and have contributed their views and experiences to a number of government enquiries and reports. But the role of lay advocacy in relation to cannabis, particularly the role of MS sufferers in the UK, has received little attention in the historical literature, despite the roles played by the Alliance for Cannabis Therapeutics and the MS Society. The nature of user activism and its impact needs closer scrutiny and opens up questions as to whether ‘respectable’ MS patients were more influential than other groups. The different groupings involved, from drug user activists in the 1960s, to the multiple sclerosis patients in the 1980s and 1990s, offer the opportunity to analyse the nature of ‘user activism’ and its impact. The thesis considers to what extent and in what ways pressure from user activists helped cannabis cross the boundary from illicit drug towards licit medicine.

‘Peculiar’ and ‘borderline’ substances

Cannabis means many things to many different people and can be framed within concepts of public health, and drug control depending on one’s view point. Some authors have provided useful avenues for research into such substances. Star and Griesemer in an historical study of Berkeley’s Museum of Vertebrate Zoology, introduced the concept of ‘boundary objects’ in relation to records or documents and showed how different groups, such as amateur collectors, professional scientists and administrators, placed different interpretations upon the same sources. ‘Boundary objects’ were able to bridge the differences between the different understanding and goals of the different groups.⁹⁵ This concept of boundary objects has been adopted for many different situations. For instance, in the medical history field it was adopted by Epstein in relation to AIDS.⁹⁶ In his study of the relationship between activism and science, he showed that a boundary object could be a virus or a medication, but, in essence, the object was one that could cross social networks, having a subtle, but significantly different meaning, depending on from where it was viewed. This concept of a border crossing substance has been considered in relation to drugs. Berridge, in her study of the shifting understandings of substances, focused on opiates and tobacco and

she showed how the boundary between licit and illicit is a shifting and negotiable one.⁹⁷ In looking at the concept of borderline objects, studies of various substances such as tobacco, opium and alcohol are useful. Berridge has provided a social history of opium tracing its development from a widely used treatment for various illnesses, and to the emergence of prohibitive legislation in the early twentieth century. She investigated some of the interests involved in the changing perceptions of opium. In relation to tobacco she considered how it portrayed an indeterminate nature – food, medicine or drug?⁹⁸ The same can be asked of cannabis. In looking at these borderline substances she considered ‘altered states’ or ‘the cultural and policy milieu’ in which drugs are regulated and the social and political factors which drive change.⁹⁹ This thesis considers the processes that altered the milieu around cannabis and its medical use. Sherratt in writing on the history of narcotics and stimulants, analysed how we define drugs, in particular, psychoactive substances, and viewed cannabis as one of a group of ‘peculiar substances’ which can cross the line from being a widely consumed substance to a dangerous drug.¹⁰⁰ Fluidity of these substances has invoked a considerable degree of controversy around them. The fluidity of this peculiar substance has been crucial in the story of the re-medicalization of cannabis.

Different methodologies have been applied to the study of cannabis ranging from standard narrative and thematic historical methods to sociological approaches. Goode took a sociological approach to looking at why we have controversies, and through a case study of cannabis investigated the impact of bias. He argued that the controversy over cannabis was due to political not scientific debate, and resultant more on previously held ideological commitments than on any new scientific arguments.¹⁰¹ Ungerleider and Andrysiak have written on bias and the cannabis researcher. They looked at the impacts on research and policy emanating from the scientists themselves, funding bodies, and the roles of industry and government. They raised the issue that chemicals have been seen as moral as well as pharmacological substances.¹⁰² Thus the existent literature goes some way in considering how we understand such ‘peculiar substances’ and raises questions as to, if cannabis is to be deemed a ‘peculiar substance,’ what is the process whereby boundaries shift between ‘drug’ and ‘medicine’ and what are the issues and interests involved in that transaction? How has cannabis’ identity as

a boundary substance, and the resultant controversies, impacted on the process of re-medicalization of cannabis and vice versa?

Cannabis within public health

Cannabis' role as a peculiar substance means it is also important to consider the process of re-medicalization within the changing natures of the frameworks within which it has been considered. Over the period under study cannabis was framed under drug control policy but also within the context of changing concepts of public health. Berridge has explored the tensions between the coercive tradition and systematic gradualism and the rise of harm reduction. It is advantageous to consider discussions of cannabis in the context of tensions in public health and drug control policies through prohibition and harm reduction.

Evidence-based medicine and the rise of the clinical trial

One of the key components largely missing in the historical literature on cannabis is the influence of the development of the clinical trial on the re-medicalization of cannabis. Historians and social scientists have shown various reasons for the growth of the Randomised Controlled Trial (RCT): the development of statistics; experimental epidemiology; the professional and organizational interests of the Medical Research Council (MRC); the relative importance of key individuals including Bradford Hill; to the consolidating influence of fears over medical technology in the 1970s that produced a climate that encouraged funding of RCTs.¹⁰³ Rosser Mathews placed the birth of modern clinical trials in the context of the search for quantification.¹⁰⁴ Tracing the developments from early nineteenth century Parisian medicine and the quest for quantification, to the rise of the British biometrical school and bacteriology, to the central role of the MRC and Bradford Hill, Mathews charted the forerunners of clinical trials to its eventual dominance. He revealed how the merging of statistics and medicine was an attempt to move medical decision-making away from an art to a science. His work raised issues of the impact of the clinical trial on the doctor-patient relationship, and ethical questions, as to where the balance lay between treating a patient and the

need to further develop scientific knowledge/treatments. The methodology of clinical trials became increasingly sophisticated, from the addition of randomization, to ‘double blinding’, and to cross-over trials. Specific developments in techniques have attracted attention, Kaptchuk, for example, has written on the development of the concept of ‘blinding’ patients and the use of placebos.¹⁰⁵ Archie Cochrane, a British medical researcher and proponent of social medicine, campaigned for more effective use of medical resources and he highlighted the importance of the randomised controlled trial.¹⁰⁶ Historians have shown how clinical trials began to impact on health policy, as well as the provision of therapeutics. Meldrum has demonstrated how RCTs became a tool of policy-making in the US where clinical trials became the route for passing medicine through the newly established Federal Drugs Agency in the post-thalidomide era.¹⁰⁷ Clinical trials have not been without their critics. Ethical considerations have always been important in clinical trials, ranging from the ethics of withholding potential treatment to concerns over the safety of participants when pushing at medical frontiers. Troth has shown in a PhD thesis on the history of clinical trials, concerns have been raised over ethics, problems of outcome measures especially in studies of pain, and the post-modernist arguments that trials can not be truly objective as they are interlocked into their social context, citing in particular, investigations into analgesics.¹⁰⁸ Questions raised in the historiography of clinical trials need to be applied to the study of cannabis. Potential cannabis drugs are dependent on successful outcomes in clinical trials and major RCTs of cannabis’ medical utility for pain and MS have been carried out since 2000 in the UK. What impact has the benchmark double-blind, randomised, cross-over trial had on the medicalization of cannabis; as well as on the delivery methods, and form of cannabis trialled and for what applications? And lastly how does a drug move from success in a clinical trial to a licensed and available medical product?

This chapter has demonstrated that there is a considerable literature on cannabis. However, this literature is focused on specific topics or chronological periods and apart from a few texts published around 2000, there is limited historical work specifically on the history of the medical use of cannabis in the UK since 1973, a period when major developments in the scientific understanding of cannabis and its medical use took place. This study therefore extends historical and social science work to focus on the

re-medicalization of cannabis in the UK in the period 1973-2004, though it also follows the story before and after as necessary, to demonstrate important changes or developments.

Existent literature was supplemented by primary research with a variety of sources which are described below.

Primary Manuscript Material

The study was heavily archival-based. The following archives were utilized.

The National Archives, (TNA)

The National Archives provided a rich source for a range of material. Records included files of the Medical Research Council, (MRC), Ministry of Health, (MH) and the Home Office, (HO). In particular, material was located on the expert groups of the Advisory Council on the Misuse of Drugs. Some material was closed under the thirty year rule and access to these files was applied for, and received, under the Freedom of Information Act.

The Wellcome Library

The Wellcome Library had considerable relevant holdings. Papers held at Wellcome included: Sir WDM Paton 1930-1993, (PPWDP). These files included personal correspondence, newspaper cuttings, minutes of committees and expert groups on cannabis. The Wellcome Library holds also the archives for the MS Society from 1953-1977.

The WHO Library and Archive

The WHO Library and Archive, Geneva provided relevant reports and documents produced by the WHO specifically on cannabis and general reports on drugs, of which cannabis was a part. These included reports on drug dependence and cannabis since

the 1950s. Although the Archive does not hold minutes of these reports it does hold other relevant documentation. Among relevant files in the Archive were: documents of the Expert Committee on Habit Forming Drugs (404-1-1), Expert Committee on Dependence Producing Drugs, (A2/81/16*) and general files on cannabis, (A2/447/c/6/J.1) and applications for research on cannabis (A2/181/11).

Personal papers

Key informants and those involved in the cannabis field proved helpful in providing additional information to that which could be located in libraries and archives, including personal papers, notes, correspondence, minutes, media cuttings and funding applications. These included papers from Professor Anita Holdcraft, Ms Claire Hodges, and Professor Roger Pertwee.

Archives of professional institutions

The archives of professional institutions, such as the Royal Pharmaceutical Society, yielded reports and minutes of the professional institutions that were involved in crucial events.

Reports and other printed material

Key reports of organizations involved were analyzed including the House of Lords, BMA, WHO, INCB, and the Department of Health. Reports and printed material were available in the DrugScope library, which is now closed. Many reports are now available on-line through the organizations' websites.

Hansard

A time-line of major events was developed early on and the parliamentary record was reviewed focusing on key events such as the debate on the House of Lords Report, and the reports of the Advisory Council on the Misuse of Drugs.

Press

Media responses were surveyed again using the time-line of major events. Reviews focused on two quality papers, (*The Times and the Guardian*); two popular dailies (*Daily Mirror and the Daily Mail*); and one Sunday paper (*The Independent on Sunday*). Other sources included periodicals, such as the *Economist*.

On-line resources

The development of the internet has added a valuable research resource. Many documents are now digitised and available to researchers on-line such as the tobacco industry documents available through the BAT archive and utilised by the Centre for Global Health, at the London School of Hygiene & Tropical Medicine. Reports and press releases are available on-line, which is particularly useful if research travel is constrained. Websites in themselves can provide a useful historical source. Many organizations, especially activist or self-help groups, can be heavily internet-based. This 'virtual world' however presents a new set of research problems. PDF files, and web pages can disappear without trace, their http address change, or simply be withdrawn. In recent years there have been calls for the archiving of websites. This is slow to arrive and would perhaps focus on larger organizations. It is possible to print webpages, but if these documents are not stored in an accessible archive, they are not necessarily accessible to researchers at a later date.

Interviews

Oral history interviewing is a useful technique for contemporary history and is a valuable means to add insight and knowledge to archival and documentary resources. Oral history provides the opportunity to gain accounts by interviewees of their experience of events. Oral history has generally focused on life histories but in recent years has expanded to develop the 'elite interview' for contemporary public health history. Virginia Berridge has used oral history techniques for a history of tobacco, as has Stuart Anderson for the history of pharmacy. Graham Smith provides a useful

history of the development of the method.¹⁰⁹ Two training courses on oral history interviewing and elite interviewing provided by the British Library and Centre for Contemporary British History were undertaken.

In social sciences more generally the aim is often to utilize random sampling techniques and anonymised interviews. Instead for this thesis interviews focused on key informants. A list of potential interviewees was drawn up and was snowballed through further research and interviewing. Interviews covered a range of actors including scientists, clinicians, science and policy figures, policy-makers, and activists. Fifteen interviews were carried out in total. Access was straightforward in most cases and participants were generous with their time.

Ethical approval for research techniques such as interviewing has become of greater importance and interest in recent years. Approval was obtained from the LSHTM Ethics Committee. Interviewees were sent an information sheet explaining the project and they were provided with a consent form which offered interviewees various ways in which their information could be utilized.¹¹⁰

Various methodologies for carrying out and analyzing interviews have been discussed.¹¹¹ The standards set by the Oral History Society were adopted. All interviews were semi-structured. A topic guide was prepared for each interviewee but the questions were left open to follow-up interesting angles generated in the interview, and or to understand the story from very different perspectives. This basic list of questions was altered throughout the research to take account of new themes and questions as they emerged from documentary and interview research. Interviews require a facilitative approach to provide a balance between probing to encourage elaboration but to avoid leading or judgemental questioning. Interviews ranged in time from thirty minutes to three hours, with careful consideration taken of the setting to take into account the needs of both the interviewee and interviewer. Interviews were recorded to provide a reliable record and future resource and then transcribed. Interviews were analyzed for key themes. Framework analysis or grounded theory of qualitative data is often used in the social sciences utilising computer programmes such

as NVivo to assist with coding and theory building. For this small number of interviews with key informants analysis was carried out by hand, highlighting emergent and interrelated themes in a method similar to that required by such computer programmes and quotes are provided in text under relevant themes. The process was iterative.

Interviews with individual key witnesses were supplemented through the organization of a witness seminar. The mechanism of a witness seminar is a useful tool to draw together those involved in a field to discuss developments, highlight tensions, debates and networks. The technique has been developed by the Institute of Contemporary British History (ICBH) and the History of Twentieth Century Medicine Group, part of the Wellcome Trust's Centre for the History of Medicine at UCL. The idea for a witness seminar on the medical use of cannabis was submitted to the Wellcome Centre which was co-organized with the Centre for History in Public Health at LSHTM, held in 2009. A topic briefing was provided for the Chairs. The seminar provided additional useful perspectives to the one-on-one interviews.¹¹²

As with any research method oral history has some constraints and in the past has faced criticism as a method. It can be limited by the availability of interviewees and especially, if interviewees are elderly, it can be difficult to carry out interviews. Issues of memory and recall are an issue for all interviewees, as is the influence of the interviewer. There are issues of bias, and the need to move beyond 'the official line'. However, such issues are not unique to oral history and can equally be a problem with printed and archival sources. Triangulation of research methods can help alleviate some of these concerns. As with all the primary data, interview material was cross-referenced with that from other interviews, the witness seminar, and documentary and archival research. The sources were weighed and assessed against hypothesis and lines of argument. Through the examination of this wide variety of source material, this thesis demonstrates the complexity of the argument around such 'peculiar' substances and seeks to contribute to a greater understanding of the process of re-medicalization beginning with the re-interest in cannabis in the late 1960s.

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Chapter Two

Understanding cannabis, 1968-1982

The early 1970s saw the development of parallel worlds around cannabis. International and national drug control policies were tightened and cannabis was dropped as a medical product by 1973. Yet, as these moves took place, scientific interest in cannabis re-emerged. A PubMed search reveals that only thirty articles referred to cannabis in the 1950s, in contrast to the one hundred and thirty published between 1960 and 1970. When cannabis was introduced to Britain as a medical product its use was limited for several reasons: an undiscovered active principle, the inability to use it within new drug delivery systems or to standardize the product, questionable efficacy and fears over its side effects. When cannabis was removed as a medical product in 1973 certain of these problems had been solved and the door was opened to the re-introduction of cannabis-based medicines. In order to understand the trajectory of research post 1973 it is necessary to review the events that took place in science, policy, funding and supply in the 1960s which enabled research into cannabis and its therapeutic potential to emerge in the 1970s. In the UK, scientists began to answer key pharmacological questions about cannabis. This chapter focuses on the role of one eminent British pharmacologist, Sir William Paton, as a means of analyzing the impact of changing scientific knowledge on the process of re-medicalization. It charts the re-emergence of interest in cannabis stimulated by breakthroughs in the understanding its chemistry, and advances in understanding its pharmacology. It considers how the growth of recreational use led to a need for a greater scientific understanding of cannabis to provide the evidence-base to underpin drug control mechanisms. It considers how hindrances to research were partially overcome which enabled laboratory research on the chemistry and pharmacology of cannabis to go forward. It concludes by considering the impact of the pharmacological research on the re-medicalization of cannabis and demonstrates how that laid the groundwork for later research into medical applications of cannabis to emerge.

Opening the door to cannabis research. The discovery of the active principle

Research into the pharmacology of cannabis took off in the 1970s primarily due to a breakthrough in understanding the chemistry of cannabis that took place in 1964. The lack of an isolated, pure active principle had been a major hindrance to cannabis' use as a medicine. The early history of research into the chemistry of cannabis and the isolation of cannabinoids has been reviewed.¹ By the late 1950s the United Nations organization, the Commission on Narcotic Drugs (CND) had called for governments to encourage research into the active principles of cannabis, most notably, to assist with the accurate and speedy identification of dangerous parts of the plant, to assist the fight against illicit traffic.² This problem was overcome by the work of medicinal chemists, Raphael Mechoulam and his group in the Hebrew University in Jerusalem, Israel. Mechoulam was interested in the chemistry and biological activity of natural products and synthetic drugs and, at the Weizmann Institute, he had investigated several natural products including cannabinoids found in cannabis. As he delved into cannabis he was surprised to find that unlike the chemistry of morphine and cocaine which were well-known, the active compounds in cannabis had never been isolated in pure form, nor was their structure really understood.³ As he worked on its chemistry, Mechoulam made a major breakthrough: the isolation of the major psychoactive principle of cannabis, delta-9-THC.⁴ This enabled him to elucidate its structure and stereochemistry.⁵ The next stage was the synthesis of the natural or phytocannabinoids. Mechoulam was able then to synthesise the active principle and THC became available both in natural form via the plant and by way of synthesis. Researchers no longer had to rely on the plant material or on extracts of cannabis with unknown constituents. THC could be produced from laboratory-made chemicals, which allowed the production of a standardized product which was crucial for research and re-medicalization. These two steps, at a time when recreational use of cannabis was increasing, sparked interest into cannabis research and opened up funding possibilities that had not previously existed. Mechoulam noted a change in funding options.

When we started nobody was interested. We couldn't get a penny to do research on it... .. The Americans told me that it's a south American

problem, we are not interested. Then everyone was interested in it, and I was supported in my research for nearly forty years by the National Institutes of Health (NIH) in the US. They were interested in the chemistry of course...we supplied them with materials in the beginning,gave them the first ten grams and on this material quite a lot of work was done in the US in the 1960s and probably the 70s.⁶

The National Institute of Drug Abuse (NIDA) created in 1972 as part of the NIH, began supplying cannabis to scientists and provided eighty-five percent of the world's research dollars for cannabis research.⁷ Despite the discovery, little else was known about cannabis and the effect of the new cannabinoids such as THC. Research was necessary on the pharmacology and epidemiology of cannabis. Furthermore, new cannabinoids posed problems for drug control policies as they were outside the control mechanisms, having been discovered subsequent to the 1961 Single Convention on Narcotic Substances.

Stimulation of cannabis research in the UK. Drug control, the MRC and Sir William Paton, 1968-1970

William Paton, a noted pharmacologist, was one of the first serious researchers in the UK to expand the pharmacological knowledge around cannabis and cannabinoids and he published significant texts throughout the 1970s. Although the method of biography and a 'great man' approach to history has its criticisms, a study of Paton's work on the pharmacology of cannabis provides a lens into understanding some of the pivotal issues around cannabis research. Paton, who kept prolific notes of his work, is important not only for his contribution to the expansion of scientific knowledge around cannabis, but because of his endeavours to transfer that knowledge to policy.

Sir William Drummond Macdonald Paton was born in Hendon in 1917, and later trained in medicine at Oxford. After successive bouts of pneumonia he moved away from the clinical field to pharmacology. He became a member of staff at the National Institute for Medical Research between 1944 and 1952 and went on to become Reader in Pharmacology at University College London and UCH Medical School between 1952 and 1954. He then became Professor of Pharmacology, at the Royal College of

Surgeons until 1959 and was made a Fellow of the Royal Society in 1956. His early work in experimental pharmacology led to important breakthroughs while he worked on methonium compounds with the pharmacologist Eleanor Zaimis and his collaboration with anaesthetist Geoffrey Organe led to important discoveries in the drug therapy of hypertension, and the pharmacology of smooth muscle relaxants.⁸ He moved on to become Professor of Pharmacology at Oxford University, and a Fellow of Balliol College between 1959 and 1984. His early work in the 1940s and 1950s had focused on decompression sickness on which he acted as a consultant to the Royal Navy. As part of this work he was interested in anaesthetic mechanisms and during his time at Oxford, Paton was able to overcome some of the problems of deep sea diving through his work on physiological properties of gases at high pressure, which led to the development of Tri-Mix (oxygen, helium and nitrogen) for divers. This interest in anaesthetic mechanisms later informed his research on cannabis. Much of his work at Oxford focused on drug dependence and in particular the pharmacology of cannabis. Sought after by government and professional bodies, he sat on over seventy committees.

Significantly for the direction of research on cannabis, he came to the study of its pharmacology via an interest in drug dependence.⁹ Concepts around drug use were fluid. They had shifted from the concept of habit forming drugs to addiction in the post-war period and they again shifted in 1964 when the WHO recommended the use of the term drug dependence rather than addiction.¹⁰ The term addiction was associated with the idea of withdrawal symptoms and the development of tolerance as seen with the use of opiates. The concept of 'dependence' merged the concepts of habituation and addiction. It was viewed as a broader model and referred to drugs which maintained some hold on the user with either physical or psychic characteristics. Prior to the 1960s, drug dependence was primarily considered in relation to alcohol and tobacco, but in the 1960s non-medical drug use of illicit drugs expanded considerably in the UK and illicit drug use became of major concern.¹¹ Paton, an early proponent of dependence, considered cannabis to be a drug of dependence of the 'psychic type'. He recognized that critics might view this as an over-reaction, *'I am sure it is true that the dependence is not normally strong and some might think I make too much of it'* but he viewed it as one of the most dangerous of the dependence producing drugs because he thought

it was innocuous enough to enter general circulation, unlike drugs such as LSD which had side-effects which he considered would deter most potential users.¹² When Paton entered the cannabis field he found only limited research on the action of the drug. When he wrote on drug dependence in 1968 he emphasized that cannabis was not understood well enough to inform policy. For this reason, in his advisory capacity he consistently pressured for the maintenance of the status quo in the legal situation around cannabis.¹³ Much of Paton's early work had been funded by his Department in Oxford but in 1969, Paton applied for and received funding for two years from the Medical Research Council (MRC) to investigate the actions and toxicity of cannabis.¹⁴ But why were Paton and the MRC interested in researching and funding cannabis research?

The incentive to study the pharmacology of cannabis was driven by drug control imperatives, not medical need, and medical use and research was constrained by control policies introduced to restrain recreational drug use. In the 1960s and 1970s the policy environment around drugs and especially cannabis was in flux. The UN Single Convention on Narcotic Drugs of 1961 simplified earlier control regimes and expanded controls to cover plants from which 'narcotic' drugs were produced.¹⁵ It was a continuation and consolidation of the 'dominant supply control mentality.'¹⁶ It introduced a scheduling system with substances placed within four schedule, Schedule I and Schedule IV representing the most restrictive. The convention meant that controlled drugs could only be used for medical and scientific purposes, though countries that had 'traditional use' were exempted for twenty-five years.

Medical use was an important delineator for placement of a drug within the system. Cannabis was drawn into this convention but its medical use had slowly been eroded. Analysis of documents and reports of the international agencies shows how, in drafting the new drug legislation, policy impacted for the first time on the medical use of cannabis.¹⁷ The documents indicate that the World Health Organization, (WHO) the health body of the UN responsible for advising the Commission on Narcotic Drugs, (CND) the central policy-making body of the UN for drug related matters, was hostile to medical cannabis. This was significant because the WHO was responsible for making recommendations to the CND on the level of international control to be applied

to 'dependence producing drugs'. In 1952 a WHO Expert Committee informed the CND that there was no justification for the medical use of cannabis.¹⁸ This decision was important for it was the first time cannabis had been officially declared to have no medical role, rather than simply falling out of widespread use. The harms of cannabis were brought to the forefront. When, in 1953 the CND asked the WHO to consider the mental and physical effect of cannabis the WHO condemned the drug unequivocally and the UN Economic and Social Council urged governments to discontinue its use as a medicine. This advice paved the way for the CND to severely curtail the use of cannabis and by 1957 the CND had requested the prohibition of all but traditional medical use.¹⁹ This was critical because it meant that when the regulatory position of cannabis was considered cannabis was differentiated from heroin and its medical derivative diamorphine, which was seen as having some medical properties despite attempts to ban its medical use.²⁰

Yet whilst these international control mechanisms around cannabis were being tightened, research on cannabis had continued and research in Eastern Europe indicated some potential medical uses, for instance, as an antibiotic.²¹ Such research filtered through to the CND which expressed concern that the draft of a planned new drug control convention might limit medical uses and as a result requested the WHO to re-examine the issue of cannabis' medical utility.²² But when the WHO reviewed the antibiotic properties of cannabis it found no reason to backtrack on its original assessment.²³ Cannabis tincture and extracts and cannabis and cannabis resin were placed in Schedule I of the Single Convention. This placed it in the same category as morphine and permitted medical use. However, cannabis and cannabis resin were also placed in Schedule IV on the grounds that medical use was 'obsolete' and its use was allegedly widespread. For Schedule IV drugs the convention required parties to prohibit, except for research purposes, cultivation, production, manufacture, export and import of, trade in, possession and use.²⁴ Penalties for misuse were left under the control of domestic laws. This led to different interpretations of the convention in different countries. But cannabis was left in a vulnerable position because its medical utility had been officially discounted by the WHO.

Governments were required to implement punitive legislation for drug misuse. It led to the establishment of the 1964 Dangerous Drugs Act in the UK and the 1965 Dangerous Drugs Act that consolidated previous legislation. This replicated the schedules of the UN convention. It regulated the import, export, manufacture and sale and possession of cannabis, morphine and opium and extended controls to cannabis and coca leaves, and by 1967 subsequent legislation had introduced police powers to stop and search drug suspects. These policy measures created incentives to better understand the drugs under control and the impact of control. Cannabis, in particular, seemed to pose a problem for legislators, especially, as in the 1960s there were large numbers of young people receiving criminal convictions, and consequently around the world commissions developed in the late 1960s and early 1970s which delved into the impact of the criminal control of cannabis use.²⁵ In the UK, where recreational use had been limited prior to the 1960s, its use increased despite increased controls and cannabis became a priority for drug regulators and expert committees.

One expert committee in particular drew attention to the problems that cannabis posed to the drug control systems. In 1967 an expert committee the Hallucinogens sub-committee of the Advisory Committee on Drug Dependence, chaired by Baroness Wootton, a leading British sociologist and criminologist, had delved into the available evidence on the pharmacological, clinical, pathological, social and legal aspects of these drugs and produced a report focused on cannabis. It raised issues that re-occurred in debates over cannabis in future decades. The Wootton report concurred that in terms of physical harm cannabis was a dangerous drug but the sub-committee questioned cannabis' relationship in terms of harm compared to other drugs both licit and illicit.

*In terms of physical harmfulness, cannabis is very much less dangerous than the opiates, amphetamines and barbiturates, and also less dangerous than alcohol.*²⁶

Moderate use was not seen as especially harmful. Flexibility in the drug control system was deemed necessary.

We do not wish to make any formal or absolute statement on a comparison of cannabis and the other drugs in common social use. All we would wish

to say is that the gradations of danger between consuming tea and coffee at one end of the scale and injecting heroin intravenously at the other, may not be permanently those which we now ascribe to particular drugs.²⁷

Furthermore, it concluded that there was no convincing evidence for the ‘gateway theory’. The report recommended that in the interests of public health it was necessary to maintain restrictions on the availability of cannabis but argued that the law should be re-cast to give more flexibility of control over individual drugs. It called for new legislation to deal separately with cannabis, isolating it from drugs such as the opiates. It questioned the perceived dangers of cannabis use and the penalties applied to cannabis under the criminal justice system.

We have no doubt that the wider use of cannabis should not be encouraged. On the other hand, we think that the dangers of its use as commonly accepted in the past and the risk of progression to opiates have been overstated, and that the existing criminal sanctions intended to curb its use are unjustifiably severe.²⁸

The report recommended that imprisonment be removed as an offence for the possession of small quantities of cannabis. In this context, police powers of stop and search were questioned and it was recommended that these powers be investigated by a sub-committee of the Advisory Committee on Drug Dependence.

Cannabis medicines were not deemed a problem by the committee. The sub-committee saw no problem with an increase in the use of cannabis as a prescribed legal medicine.

We see no objection to this and believe that any new legislation should be such as to permit its continuance.²⁹

The new synthetic versions of cannabinoids such as THC had opened up a new dimension to the debate and they were seen as worthy of investigation.³⁰ The committee’s recommendation for a re-consideration of drug policy and its call for an improved scientific base and reduction of constraints on research, stimulated research into cannabis which indirectly stimulated research into cannabis therapeutics.³¹

The Wootton report was quickly rejected by the government. Some elements of the report were accepted and the problems caused by the police powers of stop and search were viewed with concern and discussion of this aspect was passed back to the ACDD. However, the recommended reduction of penalties and a potential move toward decriminalization were rejected both for national and international reasons. The government response stated,

To reduce the penalties ...would be bound to lead people to think that the Government takes a less than serious view of the effects of drug-taking... It would be entirely contrary to Government policy to allow this impression... nor would such a view accord with the resolution of the United Nations Commission on Narcotic Drugs, which the Government accepted last year.³²

The extent to which the government could change legislation was limited since it was a signatory to the UN Single Convention on Narcotic Substances 1961. James Callaghan, the Home Secretary, whilst he rejected calls for decriminalization, did accept the need for cannabis research and called for the subsequent involvement of the Medical Research Council (MRC).

I fully accept that more comprehensive and flexible powers of control are needed to check drug abuse... We also accept that there is a need for wider research and we are bringing this to the notice of the Research Council.³³

Cannabis remained a controlled drug but the penalties associated with its use came under scrutiny in the following years and the MRC became deeply involved in cannabis research and in time the report became seen as a sensible report.³⁴

The MRC had its origins in the search for solutions to the threat of tuberculosis (TB) at the turn of the twentieth century and it had come into independent being after World War One with a remit to fund research into public health threats. When the focus of public health shifted from infectious to lifestyle disease the MRC's attention fell on the problems associated with growing recreational drug use. But its interest in psychopharmacology, a discipline that was developing by the 1970s, developed from a long standing interest in basic laboratory work.³⁵ The MRC had outlined its policy in 1969 and indicated it was,

....most anxious to foster a comprehensive research programme on the various aspects of drug dependence: worthwhile applications for support under the temporary research grant scheme for work in this field always received sympathetic consideration by the Council and indeed not insubstantial support had already been given under this scheme to various workers. In addition however there were probably a number of specific problems which could be solved relatively easily and which once identified could be carried off with Council's support on a contractual basis.³⁶

The MRC had called a conference in 1967 to determine avenues for future research and subsequently established three working parties to consider the research needs around drug dependence: the Working Party on Biochemical and Pharmacological Aspects of Drug Dependence; the Working Party on Evaluation of Different Methods of Treatment of Drug Dependence; and the Working Party on the Epidemiology of Drug Dependence.³⁷

The Working Party on Biochemical and Pharmacological Aspects of Drug Dependence which met for the first time in 1969 was chaired by Sir William Paton. It was composed of leading academics in their field, including Dr Marley, from the Institute of Psychiatry, Maudsley Hospital; Professor AH Beckett, from the Department of Pharmacy, Chelsea College; Dr Graham, at the Department of Pharmacology, at the Welsh National School for Medicine; Professor Gray, at Kings College, a Ministry of Health observer, Dr Johnston, a Scottish Home and Health Department observer, and GS Geoffrey, a Home Office observer. Its terms of reference were:

To consider the need for research on the biochemistry and pharmacology of drug dependence in particular to indicate those aspects of the problems that should be given priority or which are ripe for exploitation and to make recommendations to the council on specific research projects which should be encouraged.³⁸

During its operation it was asked to comment on some of the recommendations made by the Wootton Report. By the late 1970s there was pressure for additional drugs legislation and a draft proposal was produced. Existing legislation was seen as ‘*uncoordinated, inflexible and inadequate*’. New legislation was desired to control availability of any drug the misuse of which caused both ill effects to the individual

and which constituted a public health and social problem, ‘*and to make particular drugs subject to particular controls according to their comparative harmfulness and circumstance attaching to their misuse.*’ It was expected most of these would be pharmaceutical products with accepted medical or scientific uses but also those that might be used for non-therapeutic use.³⁹ It was not expected to apply to alcohol, tobacco, tea or coffee as Paton later queried. The Home Office prepared a confidential report and asked the MRC for comments, which, in turn, passed the report onto the Chairmen of the Sub-Committees.⁴⁰ Paton’s response to the report which was subsequently forwarded to Mr Turner at the Home Office, provides an interesting insight into the debates over the drug control framework.⁴¹

*Fundamentally I think the approach is sound and as I understand it would allow much more flexibility in dealing with a situation liable to change rather rapidly.... I find myself in a dilemma. On the one hand, I think it is probably sensible to be able to separate the more harmful from the less harmful drugs. On the other hand I am not sure that it is easy to do operationally...*⁴²

Paton raised prescient points in terms of assessing harm and the separation of drugs. Flexibility of the system he deemed important citing the changing knowledge over amphetamines. He also queried where the lines could and should be drawn between derivatives. Where, for example, would the line be drawn in the sequence of opiate based drugs? Cannabis, Paton expected, would be placed in the least harmful category.

*Finally I am sure that cannabis and derivatives would be placed in the less harmful category but of course this is only just starting and I have little doubt that synthetic cannabinoids for intravenous administration will in due course appear and since I doubt if these could be regarded as less harmful than say a casual oral dose of pentazocine one might have got things the wrong way round.*⁴³

Flexibility of movement within the drug mechanism would become of greater importance in later decades as scientific understandings expanded and the social use of drugs changed. In looking for a solution to the problem of control of drugs Paton queried if drug delivery methods were the more pressing and controllable point, ‘*accordingly I wonder whether it is possible to incorporate controls over more or less*

*harmful methods of use.*⁴⁴ The issue of drug delivery would be critical in the process of re-medicalization providing a method by which medical cannabis could be differentiated from recreational use. The development of new methods of administration of cannabis would prove equally important in the process of re-medicalization.

The Working Party on Biochemical and Pharmacological Drug Dependence looked at a variety of drugs and reported to the MRC in 1970. It had found that knowledge was lacking in many areas: the determination of drugs in body fluids; methods for detection of heroin in the blood; and the biochemistry and pharmacology of heroin in man. It became clear that cannabis was the least studied and understood drug of dependence and it was this that triggered further calls for research into cannabis.⁴⁵ One area of particular concern was the lack of reliable tests for cannabis in the blood, *'cannabis consumption is evidenced either by testimony or circumstantially; a reliable biochemical test would be of value primarily for diagnosis.'*⁴⁶ Such tests were available for morphine, cocaine and amphetamines and so research on this aspect was deemed essential in the light of penalties imposed by the Dangerous Drugs Acts. It was this that stimulated the MRC to fund and attract researchers to the cannabis field.

The Working Party on the Epidemiology of Drug Dependence was chaired by Professor M. Roth of the University Department of Psychological Medicine, Newcastle, and aimed, *'to consider the need for research on the epidemiology of drug dependence and in particular to indicate those aspects of the problem which should be given priority and to make recommendations to the Council on specific research projects which should be encouraged.'*⁴⁷ It held three meetings and also set up a subcommittee to review the supply of drugs giving rise to dependence. The working party concluded there was insufficient research directed to the problem of how and where drugs became available to the addict and that a focus on special groups such as adolescents in borstal, and young people at universities was desirable. There was also a need to develop methodology in the field, for example, simple and reliable interview schedules.⁴⁸ In a joint meeting of the working groups, prior to submission of the final reports, Roth raised the point that he wondered if the drug of dependence was unimportant and that dependence related to *'damaged personalities who would become dependent on any*

*drug.*⁴⁹ The Working Party on the Evaluation of Different Methods of Treatment of Drug Dependence, chaired by Professor AC Dornhorst of St George's Hospital Medical School focused on the treatment of heroin dependent patients as new centres for treatment offered new ways of evaluating the methods used to treat patients.⁵⁰ Once the working parties reported in 1970 they disbanded and a new working party chaired by Dr Owen was established to facilitate action on their recommendations. The interest in the biological aspects of drug dependence in relation to substances such as cannabis, nicotine and alcohol remained important and was deemed to warrant the establishment of their own working party which became the Working Party on the Biological Aspects of Drug Dependence, established in 1971. It was chaired by Paton and aimed to consider the pharmacological issues that had not been covered by earlier working groups.⁵¹ It was to consider the state of knowledge on the biochemistry and the pharmacology of dependence on drugs. It was also to identify suitable teams already working or who might work in the area and therefore to identify problems on which the MRC should contract research.⁵² The working party again pushed for further research on cannabis, most notably to ascertain the fate of cannabis in the human body, and for the development of reliable biochemical tests to assist with the criminal prosecutions. The MRC was to be critical in funding the clinical trials into therapeutic cannabis in later decades but its interest in cannabis began by funding research to improve the fundamental understandings of cannabis.⁵³

This necessitated pharmacological research. Pharmacology, the study of the effects of a drug on the body and the means by which it exerted its influence, had become the cornerstone of drug development. The British Pharmacological Society had been established in 1931 and a branch of pharmacology, psychopharmacology, had been developing since the 1950s. The discipline of pharmacology expanded in the 1960s and psychopharmacology became of greater significance in the 1970s. Berridge showed that psychopharmacology, which focuses on psychoactive substances and their chemical interaction in the brain, became important to public health and eventually re-introduced the role of 'laboratory medicine'.⁵⁴ Paton was a firm believer that pharmacology was an intrinsic route to understanding psychoactive drugs.⁵⁵ When the Wootton Report had been released in 1968 suggesting that cannabis should not be included in the Dangerous

Drugs Act, Paton, had been against these conclusions on the grounds that there was little hard scientific evidence on which to make such a decision. It was Lady Wootton's retort to Paton, '*if there isn't that much pharmacology isn't it about time you did some?*' that Gill, a colleague of Paton's, remembered triggering the Oxford group's work.⁵⁶ Paton and his team in the Department of Pharmacology at Oxford funded by the MRC would go on to carry out laboratory work and answer vital unanswered pharmacological questions around cannabis during the 1970s.

Overcoming problems of the supply of cannabis for research, 1969-1973

The availability of the cannabis tincture was important for emergent research. Controlled drugs could be made available as medicines but the 1960s had seen raised fears around the safety of licit medicinal drugs. Rachel Carson's *Silent Spring* published in 1962 had awoken people to the impact of the use of DDT.⁵⁷ The thalidomide disaster of 1962 revealed how medicines previously thought safe could pose an appalling threat to patients and this shook confidence in drug therapy and existing regulation. In the UK the government determined to exert greater control over the provision of medicine and introduced the Medicines Act of 1968 to take account of the more potent medicines developed during the therapeutic revolution of the 1950s and 1960s. This Act gave government the power to license pharmaceutical companies, products and clinical trials. The issue of the development of safety controls around medicines has been discussed by historians and it proved important in the process of re-medicalization.⁵⁸ Under this new licensing system, medicines were given 'Product Licences of Right (PLRs) which allowed drugs to be prescribed. These were granted automatically to products already on the market when the Act came into force. Controlled drugs with medicinal value therefore came under control of the Medicine Act 1968 as well. Cannabis tincture automatically received a PLR leaving it under the auspices of controlled drugs and medicines, and as such it was available to researchers. Edward Gill, a chemist who worked with Paton recalled '*there was a firm called Ransom, ... that had the country's entire stock of tincture of cannabis. So my job.. was simply to isolate a sample of pure THC.*'⁵⁹ But to isolate THC from the tincture was a time consuming process. The 1970

annual report of the MRC discussed the problem.

The extraction of significant quantities of pure derivatives from crude cannabis is a laborious undertaking and although it can be carried out in any good laboratory it is wasteful of time and manpower.⁶⁰

The synthesis of THC had partially solved the problem by providing a standardized, industrial product, but supplies of THC were difficult to obtain.⁶¹ Paton was mystified by Mechoulam's ability to source THC and he wrote in 1969,

I was fascinated by your remark about the relative availability of delta-9-THC... when I looked into it a year ago there seemed to be none available and a notable silence on the topic, it shows again how one must know where to go!⁶²

THC was not included in the 1961 Single Convention and a Home Office licence was not required for import but it still remained difficult to source.⁶³ The inclusion of cannabis in the 1961 UN Single Convention on Narcotic Substances had made the situation complicated. Mechoulam, for example, wished to send Paton some extracts but Paton had to organize licences before the material could be shipped.⁶⁴ The alternative was to circumvent the bureaucracy and risk prosecution in order to maintain an informal supply between researchers.

Problems intensified with the introduction of the 1971 Convention on Psychotropic Substances. This convention brought in more comprehensive drugs regulation that amended the 1961 Convention which had generally been seen as a compromise and as superseded by drug development such as through the development of psychotropics, non narcotic substances synthetically produced such as barbiturates, and which often rapidly entered the medical sphere.⁶⁵ The 1971 Convention kept the idea of schedules but altered their significance. Schedule 1 took the place of Schedule IV as the most stringent and included substances '*whose liability to abuse constitutes an especially serious risk to public health and which have very limited if any therapeutic usefulness.*' Parties to the 1971 Convention were required to have punishable offences but the Convention also reflected a greater focus on the study of the nature of addiction and

treatment. Thus cannabis-based drugs including phytoTHC appeared in Schedule I and parties were therefore obliged to ban them '*except for scientific and very limited medical purposes by duly authorized persons.*' Schedule I products were not acknowledged as having medical value. How this worked in practice could vary between signatories. The US, for example, had already placed cannabis in the most restrictive category Schedule I of the domestic Controlled Substances Act 1970 which included drugs deemed to be dangerous and without recognized medical use, whereas countries such as the Netherlands, Canada and some Australian states, took a more liberal approach to the treaty obligations. Britain introduced the Misuse of Drugs Act of 1971 which became the cornerstone of UK drug policy. It focused on the supply and possession of 'dangerous or otherwise harmful drugs' which became known as 'controlled drugs'. Schedule 1 of the Act created the Advisory Council on the Misuse of Drugs (ACMD) and Schedule 2 of the Act listed the controlled drugs. The Act which came into force in 1973 was complex because it had to create a balance between permitting the 'correct use' of medically or scientifically useful controlled drugs as well as preventing their misuse.⁶⁶ Under Schedule 2 of the Act controlled drugs were classified into three classes. Cannabis-based drugs such as cannabidiol (CBD) and THC were highly controlled and placed in Class A. Herbal cannabis was listed as Class B. To avoid having to amend the MDA there was provision for subordinate legislation to allow for amendments through its regulations. Regulations, for example, permitted exemptions for legitimate activities such as the medical use. Drugs were placed into Schedules under the regulations. Cannabis, certain psychoactive cannabinoids and derivatives were not deemed to have medical use and therefore they were not exempted under the regulations and were placed in the most restrictive schedule and required a licence from the Home Office for research purpose. In contrast substances such as morphine could be exempted under the regulations and did not require a licence from the Home Office for clinical trials. If a cannabis-based drug, for example, cannabidiol was to be made a commercially available licenced product the drug needed to be transferred to a less restrictive schedule of the regulations of the MDA. Cannabis medicines were no longer permitted when the Produce Licences of Right (PLRs) provided under the MCA, were reviewed and the regulations of the Misuse of Drugs Act 1971 were enacted in 1973. With no acknowledged medical use, cannabis lost its PLR and could no longer be

prescribed by doctors or dispensed by pharmacists, though it could be used for research purposes with a Home Office licence. This move meant that by 1973 cannabis came under the sole control of illicit drug regulation.

MRC funded projects ground to a halt through insufficiency of research material. A domestic source of cannabis or synthesized THC would have simplified the problem. But when the MRC attempted to encourage a commercial firm to supply cannabis under contract to the Council there was little optimism.⁶⁷ It was especially problematic because the supplies required were small-scale and likely suppliers such as Miles Laboratories refused to become involved.⁶⁸ The next avenue was to turn to an overseas source. The National Institutes of Mental Health (NIMH) in the US had begun to fund research projects into cannabis initially on the assumption it would provide an evidence base for the harms of cannabis use and underpin control policies. It was prepared to supply material free of charge. But UK researchers perceived this as a major problem as it potentially left them reliant on agreements with a foreign authority and one with its own policy and research agenda. Furthermore, the US supply of cannabis was rich in THC but lacked cannabidiol (CBD) another important component of cannabis. Paton, was deeply unconvinced about this supply chain and complained to the MRC in 1971.⁶⁹

It seems to me there is something wasteful.... I do not care for leaving the decision whether a project is worthy, not to the MRC but to NIMH... I do not consider consulting Dr Collier as adequately exploring the possibilities in industry.... if it becomes established that the MRC will not make its own arrangements for supply then there is another possibility, that they negotiate an agreement with NIMH whereby the latter makes available to the MRC a quantity for distribution at the MRC's discretion.⁷⁰

Hopes were briefly raised when it appeared that Imperial Chemical Industries (ICI) might be interested, particularly, as its Research Director, DG Davey, had been co-opted onto the MRC. But it was to no avail as ICI found the complexity of the operation did not justify the investment.⁷¹ Issues of expense and expertise waylaid other industrial alternatives. Davey had suggested an alternative – Koch Light Laboratories, a maker of industrial fine chemicals in Suffolk. Paton rejected the idea of using Koch Light on the grounds of expense, time constraints and their lack of expertise.⁷² The inability to

procure a supply left three potential sources: via the UN, through Dr Olav Braenden, Chief Scientific and Technical Section of the Division of Narcotic Drugs; from Dr Monique Braude, Acting Chief, Biomedical Section of the Centre for Studies of Narcotics and Drug Abuse, (NIMH); or via an Israeli producer, Makor Chemicals. None of these sources appeared ideal. The UN source appeared to fall by the wayside, using NIMH was advantageous in term of costs but problematic in that there were conditions attached to the supply but the Israeli source involved a commercial transaction.⁷³ As time went on the cost and practicalities outweighed the concerns of obtaining supplies from the NIMH. Paton became more resigned to a US supply though he remained dissatisfied and he wrote to the MRC of his desire to source material from Europe.

*I have reservations about the work becoming wholly centred in the USA and wish there was an adequate source of supply in Europe. But the fact is the NIMH is willing to give it away.*⁷⁴

The MRC had secured supplies from NIMH by 1972 and began to act as the central liaison and distribution point.⁷⁵ Problems arose over how to obtain the necessary import licences from the Home Office. Additionally, the solution ignored non-MRC funded researchers.⁷⁶ Although MRC researchers received their supply there remained some dissatisfaction. Researchers were irritated as they could not supply other colleagues directly and the NIMH system was viewed merely as an interim solution. When the MRC wrote to MRC researchers in 1973 to ask if they required additional material, researchers feared that the MRC wished to divest itself of this distributive role. Gill expressed his frustration with the system to the MRC.

*Research groups.....are inhibited by the difficulties in obtaining small quantities of pure materials..... research groups could approach the NIMH directly but if a body with the authority and administrative resources of the MRC find it tiresome to complete the port formalities then the burden on individual departments is even more severe. The Misuse of Drugs Act makes it illegal to provide ...with samples unless one goes to the considerable trouble of obtaining a Home Office licence....it would ...appear that the MRC is contemplating abandoning its role as an intermediary ... if that is the case it is a most unfortunate decision.*⁷⁷

Finally, the MRC agreed maintain its role and act as a clearing house for all UK requests. This was fortuitous as when in 1973, cannabis tincture's PLR was not renewed, the structure was in place for supplies of THC to enable research to continue. This early period opened the door to cannabis research, providing both incentives and systems to study cannabis. But it also revealed the serious consequences of a lack of domestic industry interest; a gap which stakeholders would prove to be keen to fill in later decades. The banning of cannabis tincture also impacted on the direction of research. Roger Pertwee, a pharmacologist and colleague of Paton in the early 1970s, recalled,

*In the early 1970s tincture of cannabis was banned. It was no longer a medicine. It had ceased. And the main interest then for research was why is cannabis bad for you? Why is it taken recreationally?*⁷⁸

Research by psychologists expanded, with researchers such as Adele Kosviner, at the Addiction Research Unit, also funded by the MRC, focused on the prevalence and impact of cannabis use amongst university students.⁷⁹ The main emphasis however remained on establishing the pharmacology of cannabis, which in this period focused on the potential harms of cannabis use.

Understanding cannabis: experimental pharmacology, the research of Sir William Paton, and the problems of cannabis use

Basic pharmacological questions remained unanswered over cannabis in the early 1970s: What was its pharmacology? What kind of impact did the structure of cannabis have? Was THC the main psychoactive ingredient? What were the physiological effects of cannabis and cannabinoids like THC? Paton argued that the role of the pharmacologist in understanding psychoactive drugs was to provide an overall description of a drug's actions to '*act as insurance against adverse reactions in human practice*'.⁸⁰ Throughout the 1970s Paton and the group at Oxford started to answer some of these questions by introducing *in-vitro* studies of cannabis. *In-vitro* studies provided a controlled environment for studying the effects of cannabis. Roger Pertwee a pharmacologist who worked closely with Paton described the initial focus of research.

Early pharmacology was descriptive because so little was known and you could go in any direction you liked and there would be new stuff to learn about what THC and cannabis were doing. A lot of interest was in confirming that THC was the main psychoactive constituent of cannabis by comparing the two pharmacologically.⁸¹

Research sought to establish the effects of cannabis and individual cannabinoids on biological systems, and compared cannabis with other drugs, and especially cannabis' ability to cause dependence.⁸² Paton and his group at Oxford published preliminary results of their research in *Nature* in 1970 in which they confirmed that THC was the main psychoactive constituent of cannabis, and they found six other pharmacological effective components of cannabis.⁸³ They discovered that the effects of cannabis ranged from lowered body temperature, catalepsy, analgesia and the extension of the sleeping time when used in combination with barbiturates. In the early 1970s cannabis' interaction with other drugs had become an important area of research. Paton and Pertwee continued to look at the effects of cannabis constituents on pentobarbitone sleeping time and phenazone metabolism. Building on the work of Professor Sigmund Loewe in the 1940s and 1950s on pharmacological studies on cannabis' structure-activity they investigated the effect of cannabis on sleep induced by certain barbiturates.⁸⁴ They researched the mechanism of action of this effect in mice and sought the constituents of cannabis responsible for this effect. Detailed results of the research were published in 1972. They found that cannabis extract prolonged sleep time and that the effect was dose-related. They concluded that cannabis extract inhibited microsomal activity of the mouse liver through the cannabidiol content. This was a significant finding because it was thought probable that human cannabis consumption could lead to interactions with other drugs, through the altered metabolism of many other drugs, not just barbiturates, taken for medicinal or recreational use.

The group developed new technology for studying cannabis. Pertwee had become interested in inert gas narcosis after doing a diving course with the military whilst at university. He went on to do his PhD under Paton on diving-caused gas narcosis and took a post-doctorate on cannabis as it appeared to act similarly to the anaesthetics.⁸⁵ Pertwee developed a new quantitative method to assay cannabis biologically: a

bioassay for cannabis. Bioassays measure the pharmacological activity of substances and were a prerequisite for establishing modes of action, a facet of cannabis that was not understood.⁸⁶ This bioassay tested the cataleptic effect of cannabis by measuring the percentage of time a mouse spent completely immobile on a horizontal wire ring. Pertwee established that responses were dose related, and concluded that THC was largely responsible and that cannabidiol had no effect. This test was demonstrated at a meeting of the British Pharmacological Society and was published in 1972.⁸⁷ This test, along with three others, was to form the Tetrad tests which became a mainstay of experiments on animals. This was significant because bioassays tended to open up new research avenues as had occurred in the tobacco and nicotine field.⁸⁸

In the early 1970s a focus was on the harmful effects of cannabis. Gill described the legislative imperative.

I think the main thrust of the work that was being done then was trying to establish there was a clear-cut case for decriminalizing cannabis. It is clearly difficult to prove a negative ie to demonstrate that THC was not harmful and one rather got the feeling that a lot of the work that was being financed was really to establish whether you could clearly demonstrate a harmful effect. If that was the case then that would really take care of the legislative problem...the stuff was dangerous so it ought to be controlled.⁸⁹

Research highlighted cannabis' potential problems and provided a degree of evidence to underpin fears that had been raised in the nineteenth century. Although cannabis was not known to cause death there were concerns over its physical effects. Paton raised fears over toxicity in a 1972 research report for the MRC. Paton found THC to be the most toxic constituent of cannabis but that other cannabinoids, such as CBD were also active and had observable effects. Animal experiments showed that the administration of cannabis caused weight loss from which some animals adapted whilst others died. Paton noted the development of tolerance to cannabis and the existence of withdrawal symptoms at high dosages in animals, though not to the same degree as to barbiturates but he felt that this could still be sufficient to predispose continued use. It was significant because tolerance and withdrawal symptoms were considered diagnostic criteria for substance dependence. Importantly, Paton's work raised fears that toxicity

was likely to be cumulative, a result of its fat-soluble (lipophilic) properties. This was seen as having serious implications for cannabis use, especially for long-term use.⁹⁰ For Paton research that appeared to show cumulative and teratogenic effects in animals meant that the use of cannabis in humans was not acceptable until there was ‘*unequivocal evidence*’ that humans were not susceptible to the effects as seen in animal research.⁹¹

Paton worked hard to publicize the results of his research and to carry his concerns to a wide audience. *Cannabis and its problems*, presented at the Royal Society of Medicine and published in the *Proceedings of the Royal Society of Medicine* in 1973, drew together a review of existing literature on the adverse effects of cannabis. Paton highlighted particular areas of concern: teratogenicity, carcinogenicity, and the impact on mental health.⁹² He expanded upon the behavioural effects on neurophysiology. These varied effects he put down to the ‘disinhibiting action’ which affected concentration and memory. In analysis of the psychopathological problems his paper raised the issue of ‘cannabis psychosis’ and he argued that though the literature on this was rarely cited in contemporary debates around cannabis, it should be taken into account. However, he did draw distinctions between ‘*effects due simply to cannabis....and exacerbation of a personality disorder, precipitation of psychosis and the exacerbation of pre-existing psychosis*’.⁹³ A key concern for Paton was the effect on young people. Work on cannabis smoking and young people had indicated neurological impacts, and Paton was particularly concerned due to the potentially cumulative effect of cannabis use on developing bodies. Some of Paton’s work was criticized for inferring effects on humans from animal studies, and the level of dosages used being greater than those that would be found in cannabis smoking. But experimental pharmacology was largely focused on animal experiments and Paton was a proponent of research on animals, and throughout his career highlighted their continued value to science.⁹⁴

Paton was troubled with the way in which pharmacological knowledge was utilized in the formation of policy. He was concerned with the inconsistency of the science-policy transfer, for example, the way in which knowledge could be applied to policy in respect to different drugs, such as in the case of cyclamates, DDT, and barbiturates. He argued,

One might venture a naïve pharmacological comment on the odd fact that cyclamates are being banned never having done any damage to any human and only with difficulty to animals, while in millions of bathroom cupboards there lie a lethal or near lethal doses of barbiturates.⁹⁵

Paton argued that for the formation of reputable policy there needed to be consistent criteria by which to assess substances, criteria which seemed to be non-existent. A few years later he reiterated this point that there seemed a split between the treatment of products developed through industrial processes, such as DDT and saccharin, which were coming under attack as dangerous products, and a natural product like cannabis, which many argued was not dangerous.⁹⁶ Paton questioned where responsibility lay for all drugs whether medical or recreational. Attitudes towards the mechanism of control of cannabis could swing between paternalism and permissiveness. For Paton, one way to avoid these extremes was to rely upon accepted principles of public health and social legislation. For a drug to be made available it needed to meet criteria similar to those used for medicine or food additives and to take into account its risks, and the number of consumers vulnerable.⁹⁷ Though Paton was not involved in some of the main expert committees of the Advisory Council on Drug Misuse of the 1970s, he tried to influence the public debate over cannabis and called for a precautionary approach to legislation in relation to cannabis. In 1978 he published an article on the impact of laboratory research on social policy. Drug policy, he argued was made up of evidence and attitudes welded together. The article case studied cannabis and considered the inter-relationship of science, medicine and policy. He saw policy decisions around cannabis as critical because he believed that they had the potential to set a precedent for the treatment of other substances.

It was with such a background that those interested in preventive medicine must consider the question of control of cannabis..., one must ask whether a government would successfully control any chemical again, if it approved for general distribution a chemical substance known to be cumulative, found to be teratogenic in three species and possessing a wide variety of biochemical and cytotoxic actions.....⁹⁸

Unlike many proponents of decriminalization, Paton attempted to draw distinctions between cannabis and other substances like tobacco and alcohol. Cannabis, he

considered, to be more dangerous than alcohol on the grounds that alcohol was ingested and therefore was not an irritant, it was usually ingested with food and was less cumulative. In contrast, he noted that cannabis was inhaled for its intoxicant effect, and was often diluted with tobacco. Cannabis could result in non-obvious intoxication, had a serious toxicology dossier, with an unknown chronic dose level, and for Paton this was of much greater concern.⁹⁹ But it was difficult to apply consistent criteria when cannabis' role in the body remained unclear.

How cannabis impacted on the body was still a mystery. A key question of pharmacology is pharmacodynamics: the explanation of how a body interacts with a drug. Understanding of the mechanism of action (MOA) of drugs was important as it also helped to explain the working of the body, for example, through the role of receptor systems. But in the 1970s the MOA of cannabis was not understood. Paton had previously worked on the mode of action of anaesthetics and he had argued that they were non-specific in action and had detailed a case for properties of fat soluble (lipophilic) substances.¹⁰⁰ In seeking the MOA, of cannabis, Paton predicted that active principles like THC which were also fat soluble had a resemblance to the anaesthetics. Pertwee found that THC mimicked the anaesthetics which seemed to support this hypothesis. It was thought that this would account for some of cannabis' actions such as hypotension, depression of cortical activity and analgesia. This led Paton to consider that cannabis, like the anaesthetics, was also non-specific in action. Such findings led Gill and another member of the team, Lawrence to argue that there was no 'goodness of fit' into a specific cannabinoid receptor and that the mode of action was quite different.¹⁰¹ This hypothesis moved research away from the idea of the specific action of cannabinoids and away from the idea that cannabis acted on receptors. Mechoulam later attributed this interpretation due a supply of impure THC and commented on the impact for cannabis research.

A very prominent group in Oxford.... had done some work on cannabis, and ... thought that its activity was not specificit was based on some work with...synthesized THC which was not very pure.so Bill Paton thought maybe these compounds act non-specifically... This was accepted... It turned out there was a mistake in the chemistry... The people who had synthesised it (had) ... not obtained very pure material. ..that blocked investigation for almost twenty years.¹⁰²

This avenue for research was not re-opened until the late 1980s when the hypothesis was disproved and a new understanding of cannabis' mode of action re-opened the cannabis field and changed the understanding of how cannabis could act as a specific therapeutic.

Paton and the therapeutic use of cannabis

Paton's concerns over the potential harms of cannabis and his fear of decriminalization contributed to his disinclination to use it as a therapeutic and he argued in 1968 that he would '*defend the case that there is no valid therapeutic use for cannabis.*'¹⁰³ He was skeptical about the anecdotal reports of cannabis' medical value. Whilst ancient and nineteenth century use of cannabis was often cited to support claims for therapeutic applications, Paton rationalized that with so few drugs available anything that offered hope was seized upon. Furthermore, cannabis as a therapeutic lacked clinical trial evidence and for Paton this meant cannabis had no contemporary proof of value.¹⁰⁴ But whilst clinical trials were the route to drug testing and licensing, large-scale trials on cannabis would not take place for decades. In this context Paton argued that there were more potent, more specific modern drugs to employ.

*Today it is proposed as an analgesic, antidepressant, hypnoticdiuretic or antibiotic, for treating glaucoma... psychiatric aid or treatment of withdrawal symptoms. For each of these uses there are more potent modern drugs. It is of greater significance that its modern rivals are also more specific, even though cannabis or THC has some particular action, its therapeutic use all entails the production tachycardia, conjunctivas, psychic changes,or depression, euphoria....its fat solubility and pharmacokinetic properties too present difficulties for sustained use, although if its toxicity were acceptable, methods could be devised for dealing with these, as with other drugs.*¹⁰⁵

Since research indicated an apparent non-specificity of cannabis, the widespread effects of cannabis were deemed a problem by Paton and a limiting factor for any medical application.

The issue of medical cannabis became politicized by the mid 1970s. Potential medical use of cannabis became caught up in campaigns for decriminalization. Lester

Grinspoon, an American psychiatrist, became an early medical activist for medical cannabis and he wrote *Marihuana Reconsidered* in which he illustrated anecdotal reports of cannabis' value as a medicine. In stark contrast to Paton he downplayed cannabis' dangers. Grinspoon had previously taken an anti-cannabis stance but, when his son who suffered from cancer found cannabis alleviated the symptoms of the chemotherapy, he began to take an altered view of the substance and became an advocate of legalization. This case and others like it raised the profile of cannabis' therapeutic potential and the need for legal flexibility to cater for patients who had no other recourse. This triggered a response from anti-decriminalization scientists such as Gabriel Nahas, an anaesthetist pharmacologist at Columbia University in the US. Paton corresponded with Nahas and they were united in their concern over the pressure that had developed for legalization in their respective countries. As with Paton, Nahas was concerned about the aspect of the debate that tried to draw cannabis closer to licit drugs like alcohol and tobacco. He commented,

*I believe that every effort has to be made to turn the tide and prevent as much as possible the widespread usage of cannabis, especially among adolescents. I am sure that it will take a good deal of time to dispel the widely spread new myth that marihuana is less toxic than alcohol or cigarettes.*¹⁰⁶

Nahas feared popular opinion was shifting against the precautionary principle that kept cannabis more closely aligned with drugs such as heroin rather than those such as alcohol.

*All these observations seem to have been performed a little too late in order to offset the momentum of the attractive but completely erroneous claims of Charles Kaplan and Grinspoon. I believe their claims correspond exactly to what many people want to hear today.*¹⁰⁷

Paton agreed with the aim of Nahas' book, *Keep off the Grass* and contributed its foreword in which he argued, 'the innocuousness of cannabis is being overstated and its dangers underestimated.'¹⁰⁸ Despite some differences of opinion Paton was pleased to see this kind of work appear.¹⁰⁹

But the book did not sell well.¹¹⁰ Popular texts on the anecdotal benefits of cannabis seemed to receive greater publicity and find a greater market. Indeed, problems with publishing cannabis texts dogged Paton.¹¹¹ Furthermore Gill recalled that ‘by the time we got to the middle of the 1970s, the effects were at best marginal, second-rate; there was no overwhelming case that could be made against cannabis on the grounds of toxicity. It was at that point that the subject lost momentum.’¹¹² Gill argued that Paton took an asymmetrical view of cannabis literature, ‘he applied all his very considerable skills to a lot of what you might call the positive evidence (ie that it was not harmful) and was much more tolerant about the negative evidence.’

Paton and Nahas feared that the claims of therapeutic use and comparisons to licit drugs such as alcohol would override research that suggested harmful effects in humans. Paton found cannabis useful for providing hints to synthesizing related molecules because of its interesting structure and not as a medicine in its own right.¹¹³ In comments to a publisher on Mechoulam’s idea for a new book on the therapeutic uses of cannabis in 1980 he argued that in light of cannabis somewhat scattergun impact on the body it was useful only as a lead.

*There is... a tendency...to show that cannabis...is therapeutically useful instead of... trying to use the hints it provides to produce some really unexceptional remedies by synthesizing related molecules. My own view is that the only therapeutic use of significance so far is as an anti-emetic in cancer therapy. Its effect in glaucoma and in bronchodilation and with cannabidiol in epilepsy ...aren't really useful as they stand... ..The significance therefore I take to be potential rather than actual for the most part.*¹¹⁴

Paton did not condemn completely cannabis as a medicine as he assumed it would be possible to deal with its cumulative problems if its toxicity was regarded as acceptable as was the case with other medical drugs.¹¹⁵ To Mechoulam he wrote of the link of therapeutic cannabis with politics.

*I was surprised that nabilone being excluded from further trial.... I still think THC points to something interesting and exploitable but its all bedeviled by politics and the pot lobbies desire for THC to be the winner.*¹¹⁶

In 1983 he commented on the dilemma,

*If your view is that it is harmless then the psychic effects and general somatic effect which would appear as side actions get discounted. If on the other hand its action and its cumulative potential have worried you in recreational use then they continued to do so in therapeutic use.*¹¹⁷

For Paton there was a considerable gap between potential therapeutic use and the advisability of using it as such.

Conclusion

At the time at which cannabis research re-emerged cannabis fell under the administration of both 'controlled' drugs and the regulation of licit medicines. But when cannabis tincture was removed as a licit medicine in 1973, cannabis was left firmly in the arena of illicit drug regulation. Whilst this move might have seemed to have ended cannabis' career as a medical substance, pressure to obtain a better understanding of cannabis as a controlled drug indirectly opened the door to re-medicalization.

The isolation and synthesis of THC, the active principle of cannabis, had removed a hindrance that had stunted cannabis' use as a pharmaceutical product, and permitted cannabis research to develop in a way that had not previously been possible. Interest originated from different scientific communities: sociologists and psychiatrists seeking to establish the epidemiology and the impact on mental and social health. Experimental pharmacologists like Paton, investigated these compounds for physiologic activity, and demonstrated various effects of cannabis. Research was mainly animal-based laboratory work. It confirmed that THC was the main psychoactive constituent but that there were a number of other previously unknown active constituents. Other significant findings indicated that cannabis could interact with other drugs, had potential toxic effects, and because of its fat-solubility could be cumulative.

Supply issues, in terms of availability, access and quality, hindered research in this period. Although problems were partially overcome, the situation was never ideal and

it drew attention to the problems encountered without a domestic supply and limited industry involvement. The quality of supply could be crucial in influencing research and the interpretation placed on research results which in turn influenced developments within the field. The lack of an independent domestic supply and industrial involvement were issues that would have to be revisited in later decades.

Nonetheless, the background knowledge to cannabis that would allow therapeutic applications to develop in later decades was explored in this period. As Paton himself explained,

*There is a misunderstanding of the role of 'basic' laboratory work. This may, if one is lucky, yield results with immediate application. But its real function is longer term, to provide the background knowledge and understanding and the rational framework in which opportunities for practical advance can be created and grasped.*¹¹⁸

By the mid-1970s many of the main chemistry and pharmacological questions had been answered. It was the interpretation of pharmacological findings in animals that was important because it raised concerns over the possible effects in humans and appeared to give credence to earlier vague fears over the harms to individuals and to society especially over mental health and long-term effects particularly to young users.

In this period science and policy became increasingly interlinked and Paton articulated concerns to the scientific community, the public and to policy-makers. The interpretation of results on laboratory animal work led Paton to campaign vigorously against the recreational use of cannabis. He emphasized the need for the precautionary principle in relation to cannabis, and pressed for preventative approaches to cannabis by the maintenance of the status quo around existing legislation. However, he also raised the need for flexibility in the mechanism of drug control, to allow for changes in knowledge.

Through international science networks Paton was aware of research into therapeutic use such as that by Mechoulam for glaucoma and epilepsy and he did see cannabis as useful as a palliative in the treatment of cancer chemotherapy. But on the whole,

Paton denied cannabis' usefulness as a medicine because of its potential long term toxic effects, and possible encouragement of recreational use but he did concede its potential usefulness as a lead. Paton's research had put into place the building blocks that would allow research into cannabis' medical applications to go forwards. Paton in a discussion of the importance of pharmacology explained,

*Pharmacology studies the response of biological system and their control by chemical substances with the special aim of improving therapeutics. Pharmacology underpins the pharmaceutical industry.*¹¹⁹

With the basic pharmacology better understood other pharmacologists began to write more positively about the drug, and clinical pharmacologists, clinicians, and the pharmaceutical industry began to study cannabis' therapeutic applications.

¹ R. Mechoulam and L. Hanus, 'A Historical Overview of Chemical Research on Cannabinoids', *Chemistry and Physics of Lipids*, 108 (2000), pp. 1-13.

² CND Resolution. IV (XII) The Question of Cannabis (New York, CND, 1957).

³ Interview with R. Mechoulam by Suzanne Taylor 2007.

⁴ R. Mechoulam and Y. Gaoni, 'A Total Synthesis of Δ^1 -Tetrahydrocannabinol, the Active Constituent of Hashish,' *J Am Chem Soc.*, 87 (1965), pp. 3273-5.

⁵ Stereochemistry: a sub-discipline of chemistry which involves the study of the relative spatial arrangement of atoms within molecules.

⁶ Interview with Roger Pertwee, by Suzanne Taylor, 24th August 2007.

⁷ Russo, *Cannabis From Pariah to Prescription*, p.2.

⁸ G. Organe, W.D.M. Paton and E. Zamis, 'Preliminary Trials of Bistrimethylammonium Decane and Pentane Diiodide (C10 and C5) in Man', *Lancet*, 1 (6540) (1949), pp. 21-23.

⁹ W.D.M. Paton, 'Drug Dependence-A Socio-Pharmacological Assessment', *Adv Sci*, 25 (124) (1968), pp. 200-12.

¹⁰ Healy, *The Creation of Psychopharmacy*; WHO, *Expert Committee on Addiction Producing Drugs* (WHO 1964), p.273; Berridge, *Marketing Health*, p. 259.

¹¹ T. Bewley, 'The Drugs Problem of the 1960s,' In J. Strang and M. Gossop (eds), *Heroin Addiction and the British System: Origins and Evolution* (Abingdon: Routledge, 2005), p. 43.

¹² The model of dependence would receive wider support in the 1980s when a broader conception of dependence was adopted. See W. Hall, *Cannabis Use and Dependence*, p. 71.

¹³ Paton, 'Drug Dependence--A Socio-Pharmacological Assessment,' pp. 200-12.

¹⁴ E. Gill speaking in a witness seminar on the re-medicalization of cannabis in Crowther, S.M., L. Reynolds and T. Tansey, *The Medicalization of Cannabis* Wellcome Witnesses To Twentieth Century Medicine (London: The Wellcome Trust Centre for the History of Medicine at UCL) in press.

¹⁵ G. Guy, B. Whittle and P. Robson, *The Medicinal Uses of Cannabis and Cannabinoids* (London: The

Pharmaceutical Press, 2004), p.390.

¹⁶ McAllister, *Drug Diplomacy in the Twentieth Century*, p. 5.

¹⁷ See appendix 4 for a diagram of the UN agencies.

¹⁸ WHO, *Expert Committee on Drugs Liable to Produce Addiction*. Third Report, in Technical Report Series, 57 (Geneva: WHO, 1952).

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²⁰ B. Whittle, G. Guy, 'Development of Cannabis-Based Medicine: Risks, Benefits and Serendipity', in Guy, Whittle and Robson (eds.), *The Medicinal Use of Cannabis and Cannabinoids*, p. 436.

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Chapter Three

Re-discovering the therapeutic use of cannabis: Clinical pharmacology and the therapeutic applications of cannabis, 1973-1982

The interest of the medical profession is slowly reviving. It is not impossible that a limited but respectable niche will be established for it (cannabis) in therapeutics by the end of the century.¹ – JDP Graham, 1976.

Whilst Paton wrote on the potential harms of cannabis a change in attitude amongst some pharmacologists towards cannabis became discernable. Pharmacologists such as JDP Graham emphasized potential therapeutic applications and questioned the interpretation of the harms of cannabis. This chapter traces the emergence of potential therapeutic applications of cannabis for glaucoma, epilepsy, as a pre-anaesthetic, and as an anti-nausea drug in cancer chemotherapy. Forces of necessity in the clinic led to some degree of acceptance of cannabis as a therapeutic. In particular, the application of cannabis as a palliative for the treatment of nausea caused by chemotherapy provided stimulus and legitimacy to the cannabis field. But whilst previous cannabis therapeutics had focused on cannabis extracts by tincture, the 1970s saw a very different focus on the form and delivery system used to confer cannabis' therapeutic properties. After the removal of cannabis tincture's Product Licence of Right (PLR) in 1973, cannabis therapeutics focused on synthetic, single entity chemicals which attempted to improve on the active principle of cannabis in order to increase its efficacy and reduce its psychoactive effect. A few small-scale clinical trials were carried out on versions of THC some of which made the leap through the regulatory processes in the US and UK. Within ten years of cannabis being removed as a medicine in the UK, the argument that cannabis had no medical value was being overturned as emergent synthetic cannabis-based drugs were licensed for limited use in the UK and US. In contrast, investigations into smoked cannabis acted as a lightning rod to controversies over cannabis, herbal medicines and smoking. Interest in cannabis' therapeutic potential infiltrated policy discussion by the 1980s with debates focused on the benefits versus

the harms of cannabis. Over this period medical cannabis remained deeply interlinked with discussion around recreational use. The newly introduced licit cannabis-based drugs were poorly tolerated by patients, and were not widely marketed as a result of the stigma around cannabis and their placement within drug control systems. In addition, public health focus began to shift away from cannabis to other illicit drugs and with no development in the understanding of the mode of action of cannabis, the field began to contract.

International research and the therapeutic use of cannabis

Whilst experimental pharmacologists such as Paton concentrated on the harms of cannabis as demonstrated in animal studies, others started to investigate cannabis' potential in the clinic. With the chemistry of cannabis better understood both pharmaceutical firms and academic laboratories began projects into cannabis-based drugs.² Two areas opened up for cannabis therapeutics: one that utilized the psychologic effects of cannabis, including its application as a sedative, analgesic, pre-anaesthetic and anti-emetic; the other that avoided the psychologic impacts and focused on cannabis as a bronchodilator, in intraocular pressure reduction, as an anti-convulsant and in tumour growth reduction.³ As is discussed in detail in chapter six, patient pressure in the US encouraged research into cannabis for glaucoma.⁴ Glaucoma is a condition of the eye in which the channels through which the fluid flows gradually become blocked, and the intraocular pressure (IOP) gradually increases causing increasing damage to the optic nerve and gradual deterioration of vision. Standard treatments were limited. Emergent reports of cannabis' benefit were largely anecdotal but some scientific research began. Hepler and Frank carried out work on cannabis smoking and intraocular pressure and found that cannabis reduced intraocular pressures in normal subjects for four to five hours with '*no indications of any deleterious effects ... on visual function or ocular structure.*'⁵ They concluded that cannabis might be more useful than conventional medications because it worked by a different mechanism. Hepler found later that when cannabis was smoked for months at a time by glaucoma patients, the effect on intraocular pressure stayed constant and there was no deterioration of vision.⁶ Mechoulam was particularly keen to push work on the

therapeutic applications of cannabis in glaucoma.⁷ He had some success with local applications of THC on rabbits for glaucoma and wrote to Paton in 1976 about his research on cannabis and glaucoma as well as epilepsy.

*We have gone ahead with the glaucoma thing but unfortunately although we have very good results in rabbits we have no idea what relevance our work has for humans. ...we are doing a double blind-clinical experiment with cannabidiol on epileptics with results so far much better than expected.*⁸

It was difficult to transfer research into the clinical environment due to a dearth of toxicity trials on cannabis and THC. Furthermore, Mechoulam's project hit snags, similar to those that had plagued Paton and the MRC in the early 1970s, that of being unable to secure industry involvement. Mechoulam complained to Paton, '*Industrial companies do not consider a new glaucoma drug worth the enormous expense of introducing it into the market so we are stuck!*'⁹ Whilst researchers demonstrated some potential applications there were only a few that were deemed worthy of research and development especially for a 'controlled' substance. Paton, for one, was not convinced over the application of cannabis for glaucoma. He responded to Mechoulam that he found it had interesting cellular effects but that interest was mainly focused on the impact on intraocular pressure and that people tended to miss the link with changes in blood pressure.¹⁰ The National Eye Institute in the US supported research studies from 1978 to 1984 in an effort to determine whether cannabis, or drugs derived from cannabis, might be effective as a treatment for glaucoma. The studies demonstrated that some derivatives of cannabis lowered intraocular pressure when administered but there were also side-effects and that they did not compete favourably with other available drugs.¹¹ Research also emerged on cannabis as an analgesic though reports were inconsistent and revealed a narrow window between beneficial and adverse effects.¹²

It was as a drug in the management of cancer that cannabis's benefits were perceived to outweigh its harms and to justify involvement in cannabis-based drug development. It was this application that contributed most to cannabis' re-medicalization during this period. The side-effects of cancer chemotherapy presented a distressing problem with new cytotoxic drugs such as Taxol causing nausea and

vomiting, sometimes to the extent that the treatment was viewed as worse than the disease.¹³ In some cases patients were forced to stop treatment. In the 1970s, it was a relatively new but increasing problem. Available cancer chemotherapy palliatives were unsatisfactory. Phenothiazine was used but its benefits diminished with use and it had unwanted side-effects. Other treatments, such as Metoclopramide, were often ineffective. As a clinically induced problem, and one that seriously limited the viability of chemotherapy as a tool, it was critical to find a solution. Anecdotal observations of cancer patients in the US had revealed that patients who used illicit herbal cannabis were less troubled by chemotherapy. Herbal cannabis, however, was in no way considered a suitable therapeutic and chemists attempted to improve the efficiency of cannabis constituents by molecular manipulation with the aim of retaining the activities of THC but without the undesirable side-effects. Mead has argued that attempts to divert patient pressure from herbal cannabis in the US during the 1970s led to research funded by the National Cancer Institute, part of the NIH, on both smoked herbal cannabis and THC. Pre-clinical and clinical research was carried out into THC delivered in tablet form.¹⁴ Sallan *et al* reported on trials with THC capsules given to twenty patients before and after chemotherapy, fourteen of whom found their symptoms of nausea were alleviated.¹⁵ Chang *et al* demonstrated that THC was superior to a placebo, and other experiments showed that it was equivalent to, if not better than, other available treatments.¹⁶ Not that it was without side-effects, some of which appeared worse than competitive drugs to clinicians, but patients seemed to prefer it. Six US states began trials that involved seven hundred and forty eight patients who smoked cannabis and three hundred and forty five who were given THC capsules. These trials indicated that smoked herbal cannabis could alleviate symptoms of nausea and vomiting following cancer chemotherapy.¹⁷ Legal restrictions made further research difficult but popular pressure led twenty one states to legislate to permit its use with cancer chemotherapy. Mechoulam, for one, was enthusiastic over this application, and viewed it as a ‘real blessing’ for chemotherapy patients, and pointed out that others found it to be the drug of choice.¹⁸ These early experiments filtered through to British researchers.

Clinical pharmacology: J.D.P. Graham and the therapeutic use of cannabis

One notable UK pharmacologist with an interest in the clinical applications of cannabis was Professor J.D.P. Graham. Graham had qualified in medicine and had developed an interest in the pharmacology of the autonomic nervous system during his time at the Nuffield Institute of Medical Research, in Oxford. After war service he had moved to Glasgow and later to Cardiff as Senior Lecturer in Pharmacology and Lecturer in Toxicology and later became Professor of Pharmacology at the Welsh National School of Medicine in Cardiff. He wrote extensively on the pharmacology of therapeutics and toxicology. He became Secretary of the British Pharmacological Society in 1961, at a time when the Society was expanding and in his role there he sought deeper links with the pharmaceutical industry. A clinical section of the British Pharmacological Society was established in 1970 and the Society introduced a new specialist publication in 1974, the *British Journal of Clinical Pharmacology*. The discipline of clinical pharmacology linked the laboratory and the clinic and assisted in the re-evaluation of cannabis as a therapeutic. Throughout the 1970s and 1980s Graham published on the study of pharmacology and the effects of cannabis on the respiratory and cardiovascular systems and its potential as a medicine in those fields.¹⁹ Graham was described as an excellent communicator and he became an influential figure in pharmacology and policy circles through his involvement in advisory committees. He became important to the process of re-medicalization not only for his research but for his advocacy of cannabis therapeutics within policy circles. One obituary in 1990 summarized his approach to life.

*Typically Scottish down to-earth approach to everybody and everything but very much his own person, not intimidated nor daunted by obstacles or difficulties but clear and decisive in pursuing the path he saw to be right.*²⁰

Graham's interest in the central nervous system led to work on narcotic analgesics, hallucinogens and drug dependence. Early work had led to structural activity profiles of α -adrenoceptor blocking agents, anti-histamines and cannabinoids.²¹ By the time he moved to Cardiff he had a particular interest in the effects of THC. Graham and his group worked by way of an MRC grant on the physiological effects of extracts

of cannabis and THC, and they studied the cardiovascular and respiratory effects of cannabis.²² Initial experiments by Graham focused on the cardiovascular effects of cannabis extracts and purified constituents of cannabis on laboratory animals including cats and rats.²³ Experiments were able to use tincture of cannabis, produced by William Ransom & Sons, from which THC was extracted. THC itself was obtained from Makor Chemicals Ltd. Results appeared to demonstrate the ability of THC to reduce systematic blood pressure, pulse and respiratory rate. Other constituents, including cannabitol and cannabidiol, were found to have no effect in rats.

Graham went on to investigate the impact of cannabis on human subjects in the clinic. Respiratory diseases, including bronchial asthma which had a rising fatality rate, were a growing problem. Early concepts of asthma as a psychosomatic disease had been overturned during the 1960s, for one with a physical component. Asthma was shown to have an inflammatory component and the search began for drugs to treat the inflammation. Pharmacology, in particular autonomic pharmacology, had become a strong field in Britain and it was important in the development of bronchodilators.²⁴ Isoprenoline had been used but had cardiac side-effects and benefits were short-lived. Other treatments included barbiturates but more effective, less harmful treatments were sought. An analogue of isoprenoline, the British salbutamol (Ventolin) was introduced in 1968.²⁵ Many of the effective therapies for asthma were originally derived from natural substances so it was not out of context to consider cannabis as a therapeutic.²⁶ Furthermore, unlike glaucoma, asthma had a high death rate, so there was pressure for the development of alternative treatments. In the US, research had shown that cannabis could cause an increase in the volume of the bronchial tubes. In the UK, Davies and Weatherstone, at the Chest Disease Research Unit, Sully Hospital, Glamorgan, Griffiths from the Department of Psychological Medicine at the Welsh National School of Medicine, Cardiff and Graham carried out small-scale double-blind clinical trials on ten volunteer asthmatic in-patients providing them with a placebo, THC, or salbutamol. The study revealed that THC and salbutamol significantly improved ventilatory function. The delivery method chosen for THC was via a metered dose by pressured aerosol, a new route of administration for THC. Nebulizers had been developed at the turn of the century using aqueous solutions, and this was superseded in the mid 1950s

by the pressurized metered dose inhaler.²⁷ By this method researchers found THC was effective in an amount too small to alter mood or be detectable by radioimmunoassay. In 1976 when they published the results of the study they concluded that THC had potential as an adjuvant medicine for asthmatics.²⁸

*The mode of action of THC differs from that of sympathomimetic drugs, and it, or a derivative, may make a suitable adjuvant in the treatment of selected asthmatics.*²⁹

The broncholidation effect of THC gained international acceptance as a potential area for cannabis therapeutics by the mid-1970s. A United Nations Office of Drug Control (UNODC) review of 1977 written by Nahas, usually more noted for his opposition to cannabis, acknowledged research in this area and accepted that it provided a novel approach, though he concluded there were problems with the method of delivery and potential side-effects.³⁰ When Graham reviewed the work on the bronchodilator actions of cannabis for Mechoulam's book *Cannabinoids as therapeutic agents* in 1982, he was able to conclude that cannabinoids had a different effect to other bronchodilators.³¹ He found that other constituents of cannabis had effects similar to THC with few cardiovascular or psychological effects, though cannabitol and cannabidiol were ineffective. In contrast inhaled THC caused an increase in airway conductance increasing the lungs capacity to absorb oxygen.³² Although this application for cannabis did not develop to the extent as cannabis for anti-nausea, the development of new delivery methods was important in the process of the re-medicalization of cannabis. Developments in metered dose, oral-mucosal spray by the British pharmaceutical industry in later decades would prove important for the delivery of cannabis extracts.

Cannabis derived anti-emetics were also an aspect of Graham's work. Earlier reports of cannabis' psychic and somatic effects, combined with numerous anecdotal reports of the effect of smoked cannabis, meant it was seen as having potential benefits for patients with incurable diseases such as bronchogenic carcinoma, undergoing radiation therapy which caused distressing side-effects. Pilot single-blind clinical trials were carried out on patients with inoperable bronchogenic carcinoma being treated by radiation and

who were suffering distress. Two groups of six patients on a cross-over pattern were investigated. Patients were administered oral THC or a placebo. Records of mood, sleep, pain, temperature and cardiovascular parameters were kept. The study found that THC caused drowsiness, improved night sleep, reduced pain, reduced elation and vigour, and increased fatigue and confusion. It caused slight tachycardia and hypotension as did the placebo.³³ Overall it was concluded that the aim to determine whether or not THC could be given readily and safely in a hospital setting and establish an active but not toxic dose had been achieved and that *'the management of stressful patients was considered to have been improved by the drug.'*³⁴ It was seen also as having wider implications for additional therapies.

*The state of passivity and relaxation shown in the above patients suggests that the anodyne (a medicine that relieves pain) may find a place in the management of patients undergoing psychologically disturbing therapy or investigation.*³⁵

With cannabis showing potential as an anti-emetic and able to ameliorate distressing medical treatments, Graham was to publicize the results of this research.

Graham was a good communicator and was keen to take the research on cannabis to a wider audience. Graham's research in the 1970s led him to take a more positive and pragmatic approach to cannabis. Whilst Paton's research led him to a cautious approach towards cannabis, Graham, though he agreed cannabis had toxic properties, played down the dangers of toxicity and its ability to cause dependence. Graham published two books on cannabis. One, *Cannabis and Health*, was an edited collection on cannabis published in 1976 to which Paton wrote the introduction. In *Cannabis and Health* Graham presented a chapter on 'if cannabis was a new drug', in which he compared it to other available licit medicines, and he argued that all medical drugs had their individual problems, and that cannabis was not unique in that respect. He pointed out that other important medicines, such as aspirin and digitalis, would not have made it to trial if they were investigated in the 1970s.³⁶ In the text he drew attention to the revival of interest by the medical profession and foresaw a time when cannabis might operate as a niche drug. As with Paton, he argued that approaches to drugs needed to

be flexible in order to take account of changing evidence. He drew attention to the fact that it was never wise to consider any drug permanently established as a therapeutic and he cited the experience of thalidomide and rauwolfia an evergreen tree from which an antihypertensive drug is made. As a clinical pharmacologist he was keen for trials to take place and argued that scientific evidence was changeable, and with that in mind, he argued that sufficient research had been carried out to justify trials on cannabinoids.

.....Insofar as the medical use of cannabis is concerned a submission would be perfectly feasible in so far as it applied to individual cannabinoid chemicals which can be produced synthetically from precursors which do not involve cultivation of the plant, in a pure form to which quality control can be applied..... most of the work for THC has been completed.There is no reason now to deny a clinical trial certificate for a single chemical.³⁷

Cannabis therapeutics, however, remained closely linked to recreational use. As seen in the different approaches between Nahas and Grinspoon in the early 1970s arguments took place over the position of cannabis in society, in particular the legal implications. Graham waded into the debate over cannabis when he wrote *Cannabis Now*, published in 1977. Graham took a rather more relaxed view than Paton about occasional, moderate use of recreational cannabis. In his book published for a non-specialist audience, he reviewed the current state of knowledge about cannabis, the history of social responses to cannabis, and the debates over its legal status. In the book, which generally received favourable reviews, Graham expounded his understanding of cannabis.³⁸

It is not a drug which causes physical dependence and only rarely is it likely to cause a complete desire for it, but one can readily become more than a little fond of it.³⁹

He accepted Paton's evidence that it could remain in the body for some time but he regarded its moderate recreational use as less of a problem.

Moderate smoking is not likely to damage the brain or destroy the personality of the smoker but it would be preferable to confine the habit to the weekends as cannabinoids linger in the body.⁴⁰

Moderation rather than prohibition and abstention was deemed a more appropriate approach by Graham, a factor he drew into policy discussions. Berridge described the two strands of public health that co-existed in the 1970s and beyond, abstention the line that Paton pursued in relation to drug use and the second, risk reduction, which became known as harm reduction and moderation of substance use, an approach favoured by Graham.⁴¹ Intent on rehabilitating cannabis as a therapeutic he tried to draw the medical use of cannabis away from the recreational debate. In his opinion, it was not cannabis per se that was dangerous, simply people's utilization of it. This was an interpretation similar in some ways to Paton's early query of proposed drug control legislation - was it more feasible to control the use or administration of a drug rather than the drug itself?

Furthermore, Graham was against the argument of denying medical use of a drug because it might drive recreational drug misuse and argued that misuse of a drug was not a reason to withhold trials.

Highly accumulative drugs such as digitalis are used therapeutically, admittedly the need for this drug digitalis is urgent, there are no alternatives.... It is by no means certain that THC will not prove to be uniquely useful as it is distinctly unusual in its actions.... a trials certificate is not usually withheld from a new drug of promise because there is potential for danger if people mishandle the drug.⁴²

Graham saw the potential benefits of a new drug for diseases which lacked effective treatments as outweighing the dangers of either its side-effects, or its potential for misuse. He posed the question as to whether the scientific community was being ultra cautious, and through fears of misuse, failed to take an opportunity of discovering a potentially unique medicine which had novel actions.

These views were important because he brought them into the policy discussions of the 1970s and 1980s. These discussions are considered in detail in chapter four, but briefly, during this period a number of governmental expert groups were set up to advise on cannabis, and divisions within the scientific communities were played out within this framework. As with Paton, Graham was involved with science-policy transfer and was a member of the Advisory Council on the Misuse of Drugs (ACMD) from its

inception in 1972 until he resigned in 1984. Whilst Paton had been at pains to argue for the legal status quo, Graham took a somewhat different philosophical approach to the discussions surrounding the law and took a very different view of the implications of toxicity.⁴³ He was cautious in accepting the right of government to impose law upon its citizens in that he felt that people should have more freedom to make up their own minds on such issues. Within the discussion of the ACMD he downplayed the dangers of cannabis, brought therapeutics into the discussion and he pressured to make changes to the law.⁴⁴ His attitudes led to heated discussions in the committee.⁴⁵ As well as being influenced by his patients, his pragmatic approach and desire for immediate action rather than the status quo was also a character trait. His desire to get things done was reflected in his committee work on cannabis in which he pressed members to be more proactive in making decisions based on available evidence rather than merely calling for more research and as a consequence delaying any decision-making.⁴⁶ These committees were significant for the process of re- medicalization as they provided an early arena for discussion on the therapeutic use of cannabis. They gave Graham, a pharmacologist with a professional interest in the therapeutic use of cannabis, a platform to influence the debate over policy. Significantly, arguments by Graham and others allowed initial attempts at drawing the discussion of cannabis therapeutics away from concerns over the misuse of drugs. This move created an environment more receptive to the re- medicalization of cannabis. Cannabis' therapeutic potential was an inconvenience to drug control policy and meant that in later decades attempts would be made to disassociate the two concepts and encouragement given to the development of licit cannabis-based medicines.

Mainstream medicine started to take more note of cannabis therapeutics. An editorial in the *Lancet* published in 1975 considered the therapeutic potential of cannabinoids and Graham's work was referenced. Though the article indicated problems and doubts about some of the research, including the development of tolerance to THC, the article raised the profile of cannabis as a legitimate therapeutic possibility. Pharmacological properties highlighted included sedation, analgesia, anticonvulsant, hypothermic and hypotensive effects, stimulation of appetite, lowering of intraocular tension, relaxation of smooth muscles, and immunosuppressive actions. The article concluded,

*THC or more probably some derivative may well find a place as an adjuvant to isoprenaline, since the action on bronchial smooth muscle differs from that of isoprenaline, or as an anodyne in the management of terminal carcinoma.*⁴⁷

The attitudes of some international organizations also showed signs of a shift. Both the UNODC and The National Institute of Drug Administration (NIDA) two agencies more noted for their hostility to cannabis acknowledged cannabis therapeutics.⁴⁸ But throughout 1970s, medical use remained largely interlinked with concerns of recreational use and impeded re-medicalization. The UNDOC report of 1977 illustrated the fears,

*If marijuana products are proven to be useful therapeutic agents, their usefulness might well be attenuated if marihuana is widely used as a recreational drug.*⁴⁹

It did, however, note that THC might be useful in the treatment of asthma, glaucoma and that cannabidiol might be useful for epilepsy. NIDA was more positive and a report published in 1976 summarized contemporary research on cannabis and in a section specifically on the therapeutic use of cannabis indicated areas of potential interest.

*Although much more testing is needed there is promise that certain of the pharmacological actions of cannabis and its derivatives can be helpful for specific conditions....The further study of cannabinoids for various therapeutic applications seems worthwhile.*⁵⁰

Possible applications noted included cannabis for use in glaucoma and for bronchodilation. Particular benefits of cannabis therapeutics were described: the cannabinoid configuration which provided a wide safety margin between effective and lethal doses and crucially, the mechanism of action which appeared to differ from known mechanisms.⁵¹ This different mechanism of action would become critical for the process of the re-medicalization of cannabis. The concept of therapeutic cannabis was back on the research agenda but it took a breakthrough in laboratory research and in understanding this mechanism to re-invigorate the process of re-medicalization. In the meantime practical difficulties and controversies remained.

Form and delivery: smoked herbal cannabis or cannabis-based derivatives

The question by the 1980s was in what form should cannabis be used. Should only one single active principle be used, or should it be synthesized or was it preferable in herbal form or was it only valuable as a lead? Paton's correspondence revealed differences of approach between different researchers within the scientific community. Frances Ames, a South African researcher who worked on cannabis with animals, found that baboons refused an extract of cannabis which forced her to work with herbal cannabis, a concept which appealed to her.⁵² Mechoulam experimented with both extracts and synthetic compounds. But on the whole, acceptance was for derivatives of cannabis rather than herbal cannabis or its extracts. Herbal cannabis was not accepted due to two concerns: its effect as an irritant and the properties of smoke. Focus fell on specific cannabinoids and the ability of synthetic chemists to modify them. In the United States, NIDA suggested that active cannabinoids could be improved, and that it should be possible to remove the psychoactive element and provide a longer shelf life. Development of synthetic derivatives without the psychoactive element and administered through alternative methods to smoking had the advantage of separating therapeutic cannabis away from recreational cannabis. At this point from NIDA's point of view there was no interest in moving cannabis or its derivatives through the drug control schedules until they had passed through the regulatory processes of the FDA.⁵³

Smoked herbal cannabis, Dr Rose and cannabis controversy

In the UK the reports of cannabis' and THC's anti-emetic properties stimulated a new avenue of clinical research and a handful of doctors applied for, and received, licences to investigate cannabis for this role in the early 1980s. On the whole research focused mainly on the provision of cannabis in the form of oral THC. Clinical researchers included Professor JS Malpas at St Bartholomew's Hospital, Dr Speed and Dr Smith from the Royal Marsden, Dr J Pritchard of Great Ormond St. and Professor JW Thompson a pharmacologist at Newcastle, all of whom were licensed to administer oral THC in a study of the psychological effects.

Interest arose also in researching herbal cannabis. As a 'peculiar substance' it was far from straightforward to carry out such cannabis research especially in a clinical environment. Clinical application was controversial not only with the continued linkage to recreational cannabis use but for technical reasons: Trialing of herbal cannabis was controversial because the method of administration was via smoking. Cannabis smoke was considered to contain many similar carcinogenic substances as tobacco smoke and there was increased opposition to smoking, the BMA for instance would begin high profile anti-smoking campaigns in 1984. The experiments of a Dr Michael Rose, a haematologist at St George's Hospital, Tooting and St James' Hospital, Balham in the 1980s, illustrate some of the controversies of researching this form of cannabis in the clinic.⁵⁴ Rose was convinced that the investigation of cannabis derivatives and herbal cannabis was worthwhile. Rose applied for a licence to study oral trials of cannabis, but later changed the application to include smoked cannabis.

The discussion became political when Rose publically complained that the legal situation constrained research and he placed public pressure on the Home Office to facilitate research. In an article in the *Lancet* in 1980 Rose argued it was time to bring cannabis back into the clinic.

*There seems to be a population of cancer patients who may benefit from treatment with cannabis derivatives...this is a pressing and important area for research. Yet, currently the Home Secretary has issued only one or two licenses for prescription of cannabis or its derivatives. I believe that failure to give cannabis to patients on cytotoxic therapy could be considered a matter of professional negligence.*⁵⁵

For Rose, cannabis research was a question for the medical profession not one for the law. In his view any problems related to the mode of administration, for instance, smoked cannabis, were technical rather than social issues. Rose complained bitterly of the effect of policy on research and medicine.

*What seems to be at issue is neither the therapeutic value nor the detrimental reputation of cannabis which have been disputed since 1839.... It is the state of public affairs which is awry.*⁵⁶

In particular Rose was irritated by the actions of the Department of Health and Social Security (DHSS). Rose argued that it was the interpretation of the law rather than the law itself that was the cause of the problems. He claimed that although the law allowed for research, problems originated from the negative attitude of the DHSS towards cannabis.

The law in the Misuse of Drugs Act 1971 makes provision for the clinical administration of cannabisthe Department of Health meanwhile without authority implicitly repudiates the public evidence of clinical potential supported no doubt by such ex cathedra sources as the British National Formulary... in which cannabis is dismissed as having no valid medical use.⁵⁷

Because of the Misuse of Drugs Act licences for research on cannabis had to be obtained from the Home Office. Dr Rose's application to the Home Office was approved after agreement by the DHSS. The DHSS agreed to permit the use of a room at Balham for the treatment to take place and cannabis derived from the plant extract was obtained from the government chemist. But in practice it proved difficult to carry out the research. Licences took time to obtain and there remained the issue of cannabis supply. Rose became upset by what he perceived as hindrances to clinical research and in particular bureaucratic wrangling. After having battled through a complicated licensing system, he continued to criticize policy and in 1981 he condemned the process in the *Lancet*.

The licence was issued after almost six months of wrangling, pursued by florid attention in the press. Having issued the licence apparently under duress the Home Office disclaimed authority to provide the cannabis indicating officials at the Department of Health as a source of supply. They in turn put it blandly thatrelease of cannabis for therapeutic purposes in the UK was more or less out of the question.

The DHSS responded that the question of therapeutic cannabis was under consideration and could not be answered in the interim. In the meantime, Rose's licence expired before he received any cannabis material.⁵⁸

The issue of therapeutic cannabis in relation to such as emotive issue as the alleviation of side-effects of chemotherapy brought into question the precautionary principle as had been advanced by Paton. Rose called this approach into question in certain circumstances.

Awaiting definitive conclusions, authorities behave with conviction that they are already available. Draconian regulation debars patients with intractable vomiting caused by chemotherapy from receiving cannabis as a potential source of relief. That seriously calls into question the claim that officialdom is acting with caution out of concern for the sick. These people are already bedeviled with problems: the calculation of risks and benefits must make allowance for their exceptional circumstances.⁵⁹

Fears of cannabis toxicity and psychosis on which this precautionary principle were based were downplayed with some asperity by Rose.

There is a disparity between the notable absence of danger associated with cannabis, and the behaviour of authority. The legions of insane, wrecked by their youthful ingestion of cannabis are not exactly in evidence.⁶⁰

The exceptional circumstance generated by cancer chemotherapy provided a wedge into the precautionary principle and increased the pressure, particularly on the Home Office and DHSS, to allow research. This placed the DHSS in awkward position. Even those individuals, who had reservations or a more cautious approach towards cannabis, considered that, in the light of constraints placed on cancer chemotherapy, the situation warranted further research. The debate continued in the *Lancet* when an editorial in 1981 observed the desperate need for new anti-emetic and acknowledged that despite problem cannabis-based drugs might have role to play.

An effective anti-emetic would revolutionize cancer chemotherapy... There must be serious reservation about the use of a drug which produces alteration in mood and perception even if these applications are likely to be beneficial to some cancer patients..... Nevertheless further studies on the anti-emetic properties of THC and related cannabis derivatives are desirable.⁶¹

Ongoing medical research called into question the scheduling of drugs. JT DuQuesne from the Psychopharmacology Research Committee, London questioned the position of cannabis and LSD and the reasons for the discouragement of research. In response in the *Lancet* in 1981, he acknowledged the need for research on cannabis.

*It is truly bizarre that cannabis is juxtaposed with lysergide (LSD) Whatever one's view of the possible adverse effect of cannabis, whether or not one believes, on the evidence, that it is habituating or holds other dangers, is it not absurd that Dr Rose and others are actively discouraged from undertaking serious clinical research, for example, such as may improve the quality of life for cancer sufferers?*⁶²

Healy has shown how a number of drugs used in psychiatry were feared as their social use was deemed to have political consequences. In the 1960s LSD also became increasingly prohibited and had been placed in the same schedule as cannabis in the US.⁶³ But in the case of cannabis the need for additional therapeutics called into question the existing policy on illicit drugs, both in relation to the inclusion and position of drugs within the control system.

These public attacks on the system and reports that also appeared in *the Guardian* and *The Doctor* provoked concern within government departments and pressure to defend government policy necessitated a note from the Chief Medical Officer to justify policy.⁶⁴ The note pointed out that cannabis was considered worthy of investigation in this instance and that four consultants in oncology held Home Office licences to evaluate the effect. It clarified the process whereby the Home Office referred to the DHSS for advice on the suitability of applicants to hold licences. Licences were granted by the Home Office, on the recommendation of the DHSS, who established the doctors' credentials and bonafide nature of research. The response highlighted problems of dealing with a drug that crossed the boundaries between a medical and recreational substance and the likely cultural acceptance of cannabis in this instance. In relation to Dr Rose it was remarked,

Officials do have some anxiety about Dr Rose and his activities but on balance it is felt that his present study is very limited and tightly controlled under Home Office regulations. There is a need to conduct studies of

*cannabis in patients with cancer and any move to revoke his HO licences would be counterproductive because of the inevitable emotive publicity this would generate. Dr Rose's activities will be closely monitored.*⁶⁵

The *Lancet* reported the position of the Minister of Health, Dr Gerard Vaughan who had been forced to respond to Rose's complaints in September 1981.

*...Dr Rose's original application to the HO was for oral trials but he later changed his research to include smoking cannabis...the HO agreed to this but requested further information... and evidence exists to indicate that smoking cannabis may be more carcinogenic than the smoking of tobacco.... The Department is not opposed to research into cannabis or its therapeutic potential but there are constraints under the law and a responsibility to avoid harmful side-effects.*⁶⁶

The route of administration was a key factor in the debate over medical use of cannabis. It seemed that orally administered, extracts of cannabis or synthetic THC in exceptional circumstances were acceptable but smoked herbal cannabis was a step too far, especially in light of the anti-smoking campaigns. Graham and Rose corresponded over the mode of administration of cannabis. Rose wondered if the aerosol method used in Graham's research with asthmatics would be transferable for anti-emetic purposes.⁶⁷ Developments in drug delivery systems remained important for the process of re-medicalization and were further developed in the 1990s.

The process was confusing for researchers such as Paton and Mechoulam. In 1981 Mechoulam wrote to Paton that he had several hundred grams of cannabidiol but that he found it difficult to initiate trials for epilepsy and he asked Paton if there were suitable groups in England that might be interested. Paton wrote to the Home Office, and the query was forwarded to the DHSS.⁶⁸ The DHSS explained the system. There were two route to research. The more usual system was for researchers to apply to the Home Office for a licence to possess and administer the drug. Such requests were then forwarded to the DHSS who considered the suitability of the research worker and project design before licences were issued by the Home Office. Alternatively, if the Department wished to promote research in a particular field suitable research workers would be informed and encouraged to submit protocols. But this route was for areas of

priority and *'until the Minister has received recommendations of the Advisory Council regarding the priority of research into the therapeutic potential of cannabis the latter procedure could not be initiated.'*⁶⁹ As is discussed in chapter four the ACMD did give later cautious consideration to the therapeutic benefits of cannabis as growing acceptance of synthetic cannabis-based drugs offered greater legitimacy to the concept of cannabis as a medicine.

Cannabis derivatives become licenced medicines

Urgent necessity to alleviate symptoms which were in themselves being created by medical intervention meant that cannabis as a therapeutic was given a legitimate role beyond that of a drug of misuse. Suggestions for the study of extracts of cannabis or synthetic THC instead were extended. Whilst researchers were able to carry out research on cannabinoids for various applications to bring cannabinoids to patients on a large-scale was another matter. Any cannabis-based medicine required a licence from regulatory bodies, at that time the Medicines Control Agency in the UK or in the US, the Federal Drug Administration (FDA). Unlike the trials of cannabis for respiratory and cardiovascular problems which did not lead to a licenced medicine, it was for the alleviation of symptoms caused by cancer chemotherapy that licenced cannabis-based drugs were produced.

Synthetic THC presented the acceptable solution. A single chemical entity, orally administered version of THC was able to pass through regulatory systems in the US and UK. The pharmaceutical company Eli Lilly brought to market, nabilone, an analogue of THC, branded as Cesamet and targeted at cancer chemotherapy patients.⁷⁰ As an analogue of THC it was hoped nabilone would avoid the psychoactive properties of THC, and the associated concerns over misuse. The role of industry in bringing nabilone to market is detailed in chapter five but nabilone was licensed in 1982 for prescription-only hospital-only use against nausea arising from chemotherapy and unresponsive to other treatment in the UK and was licenced in the US by the FDA in 1985. It appeared initially to offer an acceptable way forward. As Leslie Iverson, a pharmacologist with an interest in policy later explained,

The result of properly controlled clinical trials in the 1970s and 1980s indicated that the two cannabinoid drugs, dronabinol and nabilone appeared to offer an potential important advance over the relative ineffective anti-sickness medicine available in the 1980s.⁷¹

Nabilone was not widely marketed and was withdrawn in 1989 in the US although it remained available in the UK and Canada. Another drug, dronabinol (Marinol) synthetic THC, was given approval by the FDA for treatment of nausea in cancer chemotherapy in 1985. Marinol was never marketed in the UK. A decade after the removal of all cannabis-based medicines, cannabis derivatives based on the active psychoactive principle of cannabis, THC, were back in the medicine cabinet.⁷²

These derivatives had significant problems. The psychoactive effects which could not be totally avoided, remained of concern to doctors and patients, and this constrained their application. They proved unpopular with patients for several reason including, the ‘high’ produced as a side-effect, and the time lag between administration and effect. In addition their use was heavily restricted due to fears over potential diversion to recreational use. Competitor drugs emerged quickly, ones that were more effective, soluble in water and therefore usable as an IV injection at the time of therapy: a preferable administration method for patients with nausea. Furthermore, with no progress on the mode of action of cannabis, no one really understood how these drugs worked. However, despite their problems and limited uptake, the arrival of these synthetic cannabinoids into the clinic was critical for the process of re-medicalization. It marked the re-introduction of licensed cannabis-based medicines, and provided cannabis research with a degree of legitimacy which encouraged further investigation of cannabis from a therapeutic viewpoint rather than a continued focus on its deleterious effects. It also left the potential for research into herbal cannabis in later decades.

The temporary slowdown in the cannabis field

The sudden surge of interest in the pharmacology of cannabis that had developed from the 1960s proved short-lived and by the late 1970s and for most of the 1980s, the field ceased to develop. Pertwee described meetings of the British Pharmacological Society

in which cannabis was essentially ignored, with cannabis posters being relegated to the sidelines and cannabis talks to the last session of the last day. He commented later, ‘No one was interested. ‘Why work on cannabis?’ was a constant question. It got a bit depressing.’⁷³ One problem was the absence of dedicated cannabis research societies and only occasional symposia which failed to motivate the discipline. Pertwee recalled,

*In the 1970s and 1980s there weren’t any cannabis societies and there’d be the occasional symposia, but many of those were organised in a way that you always had the same speakers. It was all very constrained...it wasn’t very encouraging for the development of the field.*⁷⁴

Work had become descriptive, centred on the chemistry and pharmacology but, without any advance in understanding the mode of action, there was little opportunity to carry out exciting new research. Pertwee described the situation.

*We had run out of things to do. Very descriptive, just describing the pharmacology. There was no handle on the mode of action.... All pharma was thinking about cannabis and then abandoning it.*⁷⁵

The report by NIDA in 1977 indicated the potential importance of discovering cannabis’ mode of action for research and medicine.

*In addition to the possibility that therapeutic benefits may one day accrue another reason for studying the potential medicinal value of the cannabinoids is the possibility that their mechanism of action may be different from the currently available medicaments. In this case the elucidation of these mechanisms would be even more significant than the mere discovery of another therapeutic agent.*⁷⁶

Without a breakthrough in the mode of action the cannabis field began to contract as many researchers and funders switched to other fields. Furthermore, the cannabis threat was being superseded by other concerns including ‘hard’ drugs such as cocaine and heroin, and new public health fears over the emerging disease of AIDS. Additionally, interest shifted away from drugs such as cannabis to a greater focus on licit drugs including alcohol and tobacco. The Addiction Review Group of the MRC in 1978 concluded, ‘in view of the adequate amount of work on the pharmacology of addictive

drugs there was no need to specifically encourage more in the future’⁷⁷ By the 1980s comments in the House of Commons highlighted the economic and social costs of alcohol and tobacco as opposed to the illegal drugs.⁷⁸ Pertwee recalled the shift and the impact of changed incentives for researchers.

*People were running out of things to do and the thing was winding down, people were leaving the field...going into amphetamines, or dependence, or ecstasy... other drugs of dependence, especially in the States. They couldn't get funding basically, on cannabinoids.*⁷⁹

The process of re-medicalization was affected as well. Paton's analysis when he acted as a referee to Mechoulam's book *Cannabinoids as therapeutic agents* summed up the altered environment.

*One should resist the book being too long. I might add that I think there would be a reasonable but not enormous sale. I think the cannabis field is getting less fashionable.*⁸⁰

Some individual researchers including Mechoulam and Pertwee maintained their own enduring interest in cannabis despite the general trend. This continued interest proved important for later developments in the cannabis arena. Pertwee later described his reasons to remain in a diminished field.

*I stuck with it and decided to develop this assay. I just felt it useful to have. Very lucky for me that the receptor was discovered and I could be in at an early stage.*⁸¹

Pertwee had moved from Oxford to Aberdeen to establish another research “cell” in 1974.⁸² For his research he drew upon work in the opioid field. Hans Kosterlitz and his team who became famous for their discovery of opioid receptors in the brain and the endogenous morphine-like substance which they termed enkephalins were based at Aberdeen.⁸³ This discovery explained why opiate worked. The discovery of the opioid receptor proved important for the concept of addiction and borderline substances like tobacco. This research eventually provided the rationale for understanding how the brain deals with pain and enabled the production of new analgesics. The techniques

for research used by Kosterlitz were important to cannabis research. Kosterlitz worked on opium using mouse vas deferens.⁸⁴ Pertwee's experiments examined whether this process could be applied as a bioassay in the cannabis field and his research later proved fortuitous as it turned out to be a sensitive assay for the cannabis agonists that were developed later in the 1990s. As with the discovery of opioid receptors, a breakthrough in cannabis' mode of action and the discovery of cannabinoid receptors in the late 1980s would re-awaken the cannabis field and open up new avenues for cannabis research, and lead to new understanding of how the human body functioned.

Conclusion

Within a decade of the banning of cannabis tincture, cannabis-based drugs were back in the clinic. Pharmacologists provided a more detailed understanding of the pharmacology of cannabis itself and initiated more positive approaches to cannabis with discussion of its potential therapeutic benefits. Numerous potential applications were investigated but it was as a bronchodilator, an anti-emetic and for glaucoma that became the most widely accepted avenues. Focus fell not on 'whole cannabis' but on synthetic, single chemical entities, derived from cannabis, like THC. Synthetic cannabis-based products re-opened the therapeutic arena as they appeared to offer a way to improve the efficacy of cannabis and at the same time reduce undesirable side-effects. The search for solutions to new clinical problems related to cancer chemotherapy saw the move from anecdotal to evidence-based medicine with the provision of larger-scale clinical trials. Some clinicians such as Dr Rose pressed for investigation of herbal cannabis, but the use of smoked cannabis as the delivery method meant the use of herbal cannabis was interlaced with controversy. Clinical pharmacologists, like Graham expounded the potential benefits and played down the dangers of cannabis use and took this viewpoint to both policy-makers and the public. Even researchers with a more cautious approach like Paton and Nahas recognized the potential therapeutic avenues. As is discussed in the following chapter, expert groups in the UK began to take note of the importance of this developing area. But the perceived interaction between medical and recreational use remained a major stumbling block to medical use. Whilst sustained interest in cannabis therapeutics would not re-emerge until the late 1990s the period of

the mid-1970s to late 1980s re-awoke the concept of cannabis as a medicine. and began to overturn the WHO's 1951 pronouncement that cannabis had no medicinal value. Importantly, whilst cannabis remained firmly routed in illicit drug regulation cannabis derivatives through the involvement of the pharmaceutical industry re-entered the licit medical drug arena through the licensing of two cannabis-based drugs in the 1980s. As Paton had predicted cannabis acted as a lead to other drugs not as a drug in its own right. These, as pharmaceutically produced substances, entered drug control regulation and were still tightly controlled and rarely used, which left the door open to further industry involvement, the investigation of 'herbal cannabis', and patient pressure for access to herbal cannabis. It would take sustained pharmaceutical industry involvement and a breakthrough in understanding cannabis' mode of action to revitalise the cannabis field and lead to the next steps in the process of the re-medicalization.

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- ⁷⁰ Analogue: A drug that's structure is similar to the structure of another drug but whose chemical and biological properties may be different.
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⁷³ Interview with R. Pertwee.

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Chapter Four

Evidence-based policy? The development of expert committees and the re-medicalization of cannabis 1972-1982

During the time that research into cannabis and its therapeutic applications was emerging, moves were taking place to make policy more evidence-based and this chapter traces the re-medicalization of cannabis within the context of the development of expert advice. Historical research has shown that *'the idea of rationality, that there could a rational relationship between research and policy was high on the agenda,'* by the 1970s.¹ Berridge demonstrated how this trend impacted on dealing with both licit and illicit drugs, and where policy was in flux. She reveals how this shift in government advisory mechanisms opened doors between government and professional bodies allowing for interactions between specialists and policy-makers.² Evidence-based policy became the goal, emerging through a mechanism of expert committees, which formalized previous informal networks of advice. In the drugs field, previous ad hoc committees were reconstituted in 1972 as the statutory Advisory Council on the Misuse of Drugs (ACMD) with the aim of providing advice to government on drugs of misuse. This mechanism of an institutionalized statutory expert committee became an important forum for policy discussion around cannabis. Around the time the ACMD sub-committees on cannabis were created, cannabis, which had previously come under the jurisdiction of both illicit drugs and licit medicines, lost its 'product licence of right' and had become solely aligned with drugs of misuse. However, as research re-emerged on therapeutic use the implications of this research were drawn into the discussions over drug control policy and the expert committees became an early arena for discussion of the therapeutic use of cannabis prior to the therapeutic specific discussions and public reports of the 1990s. Three significant deliberations are considered in this chapter. The first of these was the ACMD's Working Group on Cannabis, 1972-76 which discussed research gaps, and legal issues and produced two interim reports. It saw animated discussion between committee members over the relative harms of cannabis and had the occasional reference to research on therapeutic cannabis. The second committee

studied was the ACMD's Working Group on Cannabis, 1977-1979, which focused on the impact of potential amendments to the Misuse of Drugs Act through proposed amendments to a Criminal Law bill. Its discussions led to a decision to recommend the downgrading of cannabis from Class B to Class C. The decision was based on heated and divisive discussions over the position of cannabis in the control system and the relative dangers of cannabis. The final committee considered was the ACMD's Expert Working Group on Cannabis, 1980-82. This group had a new membership, was less acrimonious and discussion of cannabis therapeutics featured more prominently, influenced, in part, by clinical trials of cannabis for the treatment of the side-effects of cancer chemotherapy. When the Expert Working Group on Cannabis released its report in 1982, it, too, recommended the downgrading of cannabis, and the encouragement of research into cannabis as a medicine.³ This chapter considers how these expert groups were established, the impact of their membership, the impact of therapeutic cannabis and it tracks the evolving discussion over therapeutic cannabis within the broader drug policy debate.

The Advisory Council on the Misuse of Drugs and the Working Group on Cannabis, 1972-1976

During the 1950s and 1960s expert committees had been established in the illicit drugs field on an ad hoc basis. The DHSS at the request of the Home Office set up the Interdepartmental Committee on Drug Addiction in 1958 to update advice given by the Departmental Committee on Morphine and Heroin Addiction in 1926 and to advise on the use of dangerous drugs of addiction.⁴ Chaired by Sir Russell (later Lord) Brain, President of the Royal College of Physicians, its brief had been to consider whether any revised advice should cover drugs liable to produce addiction or to be habit-forming; to consider whether there was a medical need to provide special, including institutional, treatment outside the resources already available for persons addicted to drugs; and to make recommendations, including proposals for any administrative measures that might seem expedient. The committee reported in 1960 and came down in favour of the status quo concluding that, in view of the small number of drug addicts in the UK, further restrictions on heroin and cocaine were not necessary. The committee's

report looked briefly at the issue of the medical use of cannabis and concurred with the WHO's position that cannabis had practically no therapeutic use and its control was not a medical matter within the committee's terms of reference.⁵ This acceptance of no medical utility was important for the later placement of cannabis within regulatory mechanisms, differentiating it from heavily controlled drugs like morphine which were seen to have medical benefit. By the time of the second Brain report of 1965 growth in recreational drug use had led to a perceived need for greater drug control, and as a signatory to the 1961 UN Single Convention on Narcotic Substances, Britain had enacted the 1965 Dangerous Drugs Act.⁶ The Brain report recommended the creation of an advisory committee, to advise government on the social and medical aspects of drug use. In this context, an ad hoc body, the Advisory Committee on Drug Dependence (ACDD) was set up under Sir Edward Wayne, Regius Professor of the Practice of Medicine at the University of Glasgow. Sub-committees investigated specific drugs and, as discussed in chapter two, the Wootton Committee had focused primarily on cannabis. When the international framework around illicit drugs was tightened with the 1971 Psychotropic Drugs Convention, corresponding alterations to UK policy were required and resulted in the Misuse of Drugs Act 1971. With the need for an on-going specialist advisory body the earlier, ad hoc Advisory Committee on Drug Dependence was refigured as a statutory body and renamed the Advisory Council on the Misuse of Drugs. Its remit was to:

Keep under review the situation in the United Kingdom with respect to drugs which are being or appear to them likely to be misused and of which the misuse is having or appears to them capable of having harmful effects sufficient to constitute a social problem, and to give to any one or more of the Ministers, where either Council consider it expedient to do so or they are consulted by the Minister or Ministers in question, advice on measures (whether or not involving alteration of the law) which in the opinion of the Council ought to be taken for preventing the misuse of such drugs or dealing with social problems connected with their misuse, and in particular on measures which in the opinion of the Council, ought to be taken.⁷

The creation of the Council was an important development. Griffith Edwards, an eminent researcher on drugs and alcohol and a member of the ACMD later explained the power of the Council.

A statutory organization; its existence is embedded in the Misuse of Drugs Act so even when Mrs Thatcher was trying to get rid of QUANGOs (quasi-autonomous non-governmental organizations) she couldn't touch it.⁸

Members of the committee were Home Office appointments. Ministers were obliged to consult the ACMD before laying Orders before Parliament or before making Regulations under the Misuse of Drugs Act, though they did not have to act upon its advice. It necessitated a working relationship between experts and government. However, from the time of its inception this was an uneasy relationship.

Cannabis was a major initial feature of the ACMD's work, although other drugs were investigated. Edwards recalled in 2009 how the Advisory Council became enmeshed with cannabis.

The Advisory Council on the Misuse of Drugs was not a cutting edge organization for its efficiency and it could take six years for any working party to report. It got bogged down with cannabis.⁹

The ACMD created a sub-group, the Working Group on Cannabis to advise the Council on cannabis in late 1972. Whilst the role of the ACMD was to provide expert advice, the available evidence on which to formulate any advice was limited. In essence the Working Group on Cannabis set out to investigate some of the major questions raised by the Wootton Report of 1968, including the harms associated with cannabis use, and the role and impact of criminal sanctions, especially police powers of stop and search. Cannabis policy and its implications were high on the agenda. A major focus of discussion was the legal situation around cannabis. Cannabis had been placed in Class B of the Misuse of Drug Act 1971, with a resultant set of penalties. Its placement had proved controversial and there were calls for decriminalization, either by changing the position of cannabis in the classes or by altering the penalties associated with each class. Measures for cannabis control that had emerged such as stop and search were particularly inflammatory and became a key area of debate for the Working Group on Cannabis.

The membership of the working group was important and brought together experts from the different sides of the debate. Berridge described how expert committees including the ACMD were viewed as part of the *'polite and gentlemanly relationships out of the public view which characterized government-medical interactions in health policy'* but she made the additional point that as expert committees developed, they began to incorporate expertise from within and from outside government, and emphasis was placed on technical expertise and the role of research.¹⁰ Members in this instance included: Bob Searchfield, a sociologist, and Director of the Standing Conference on Drug Abuse; Griffith Edwards, Director of the Addiction Research Unit, at the Institute of Psychiatry and JDP Graham who had sat on the Wootton Committee and whose pharmacological research into cannabis was examined in chapter three. The working group was chaired by Mr JC Bloomfield, a pharmacist. The composition of the working group proved critical to the way in which the discussions were framed. Expert advice of the period has been described as a mixture of *'the great and the good'* with limited politicization and based on an *'ethic of politeness'* but behind this, at least in relation to cannabis, lay critical differences in approach.¹¹ The different professional backgrounds of the members meant that behind the Working Group on Cannabis' reports lay mixed messages and different approaches, to both the scientific evidence around cannabis and the interpretation of what to do with such evidence. The working group comprised of strong personalities and reflected both sides of the debate. Graham, influenced by his research and perhaps the immediate needs of his patients, took a more benign view of cannabis and was keen to draw conclusions and make recommendations for action. One obituary described his forthright personality and approach to life.

*Jimmy was an energetic and forceful character. Always eager to get things done now rather than later. He was frank and forthright, blunt even. And would become impatient and even on occasion impetuous when, in his view, events were unnecessarily hindered by bureaucracy or more cautious individuals. These qualities were appreciated and endeared him to kindred spirits but occasionally rendered him vulnerable to those holding influential positions.*¹²

Edwards later described Graham's approach to cannabis as, *'asymmetry personified- he believed that cannabis should be legalized.'*¹³ In contrast, Edwards was against

liberalization and reflected Paton's more precautionary approach to cannabis and its potential harms.

The working group met for the first time on the 1st of December 1972 and between 1973 and 1976 produced two interim reports. The initial work was essentially an information gathering exercise to clarify basic information about cannabis and its use in the UK by examining current literature, analyzing the consequences of cannabis use for individuals and society, establishing what research was in progress and general epidemiological details.¹⁴ As discussed in the previous chapters, pharmacological cannabis research in the 1960s and early 1970s was primarily focused on animal research and the deleterious effects of cannabis. The impact on humans required a stronger evidence base. Reports presented to the working group, such as a paper by Graham in 1973 on the harms of cannabis use, indicated that research was still required on drug interactions, reproduction, and neurological damage.¹⁵

The working group had been established to consider facts relevant to the use of cannabis and other psychedelic drugs not normally in therapeutic use and to examine the need for further research. It was not constituted to report to ministers at this point but was rather set to provide the ACMD with a better understanding of cannabis in the context of growing international and domestic campaigns for a relaxation of controls on the drug. At the first meeting the group decided to consider the current literature on cannabis, its use within the UK, and the form and presentation of the debate on cannabis. Edwards attempted to introduce a consistent framework by which cannabis could be assessed and this informed much of the follow-up discussions. He presented a paper entitled, *Cannabis and the criteria for legalization of a currently prohibited recreational drug* in 1973.¹⁶ The paper identified criteria which might be employed to consider whether any drug should be legalized and applied them to cannabis. Edwards placed discussion of cannabis within the context of the rise of regulatory frameworks controlling drugs, increased control of food additives, and a heightened awareness of previously under-rated dangers of already accepted substances. Edwards argued that stringent new regulations represented changed attitudes towards all drugs.

*A move towards legalization of cannabis will be subjected to far more rigorous scientific and political scrutiny than would have been the case before 1963.*¹⁷

Within this context he argued that legalization of cannabis could not be justified, and indeed legalization was never on the agenda for the working group. Instead the question hinged upon how cannabis could be prohibited without bringing the law into disrepute; a major problem with an illicit but borderline substance. Discussion in the fifth meeting focused on the impact of control measures. Attitudes to the legal situation varied. On the one hand, Searchfield was concerned over the immediate impact of the social effects of penalties on individuals, such as fines for poorer members of the community. He argued that the use of 'drug squads' and increased numbers of arrests simply polarized positions, and that the '*day to day social damage to individuals which was occurring as a result of prison sentences for first and seemingly trivial offences should not be overlooked*'.¹⁸ On the other hand, Edwards, although he recognized injustices should be eliminated, was more concerned with the public health threat over a longer term. Edwards framed the question as a public health concern but one which necessitated a coercive legal framework.

*The Council's work was concerned with the long-term. Present injustices moreover might seem slight in relation to the possibility of irreversible health damage on a large-scale.*¹⁹

The indeterminate nature of cannabis was reflected in the discourse of the working group. Though it was classified as a drug of misuse, research both in the UK and abroad had begun to raise the question as to whether cannabis should be viewed once again as a therapeutic drug. Therapeutic use of cannabis, which was being investigated by the broader scientific community, entered into discussions in this period to a limited degree both in its own right and as an adjunct to discussions around cannabis controls. Here the composition of the working group was important. Graham brought various areas of research to the attention members including his own work on the physiological effects of extracts of cannabis and of THC, as well as Paton's work on the effect of cannabis on the immune response, and other studies that had found cannabis to be an antipyretic as well as the need to look for therapeutic possibilities of cannabis.²⁰ Whilst the

potential of therapeutic cannabis had become more acceptable, the advisability of the application of cannabis therapeutics was disputed because of perceived risks and moral implications. Edwards had taken note of the therapeutic research in his 1973 paper but he questioned where the balance between benefits and risks lay.²¹ Like Paton, Edwards was concerned with the broader effects of using it as a medicine and commented in a meeting in 1973.

*It was not per se a drug without therapeutic possibilities, such risk of damage as might be found shouldbe weighed against any known benefit. Three areas would need to be examined, acute toxicity, chronic toxicity and any public health hazards envisaged as a result of the foreseen prevalence and frequency of use.*²²

A related issue that was raised in these early discussions and one that would later prove important for the therapeutic use of cannabis was the form in which cannabis might be utilized as a medicine. Splitting cannabis into its constituent parts was one method of moving re-medicalization forward. Standardized THC was deemed acceptable, herbal cannabis was not. In discussion, Dr Cahal from the DHSS drew attention to the lack of standardization of herbal cannabis, but he argued that THC should be approached as any new drug and that if indications of therapeutic qualities existed then clinical trials should be carried out to test its efficacy and safety.²³

The Working Group on Cannabis produced its first interim report in 1973 which was approved by the ACMD which agreed that the report should be submitted to Ministers. The report considered the extent to which cannabis was harmful in terms of physiological and social effects, highlighted areas lacking in cannabis research and made recommendations for further research.²⁴ Eight areas of research were to be encouraged: pharmacology of the constituents of cannabis and their interactions with other drugs; development of body fluid assay techniques; dependence potential; prevalence of use and characteristics of the user; association between cannabis and brain damage; identification of possible functional mental syndromes; the psychopharmacology of cannabis use and the impact on controls; as well as carcinogenic and teratogenic properties. The report was significant because it demonstrated the level of uncertainty around cannabis and therefore the inability of the

working group, and therefore the ACMD, to provide expert advice on issues of control. It concluded,

Our study confirmed the case for alleviating the controls on cannabis is fraught with uncertainty, even if minor constituents were deemed safe many of the effects of prolonged and widespread use would remain. There is no likelihood of significant changes to the pattern of control until some of these uncertainties have been resolved... the possibility that over-restrictive controls may give rise to social damage ...individuals and society can not be overlooked... For present the aim of report is to draw attention to the need for research and give urgent consideration to stimulating research.²⁵

But calls for further research on cannabis created concerns within the ACMD and policy circles that these conclusions, if made public and/or if acted upon, would generate the wrong message and boost calls for legalization. These discussions in the 1970s were intended to be kept out of the public domain, an approach that was not unusual at this time. Edwards and the chair were content to leave the report in the private arena, whilst Searchfield who tended to be in favour of legalization was keen to make the report public. Graham saw no problem in publication but did not make an issue of the point. The fear that the public might misunderstand the advice has been an often repeated explanation for the reasons for government rejecting expert advice on cannabis from the 1970s onwards. As Jasanoff has shown that the 'evidence' of expert committees can be socially constructed and is not value free.²⁶ Certainly concern over social factors and wider debates over cannabis were embedded in the members' discussions. Fear of the media and the public response was the background to much of the discussion.

Certain aspects of research were especially contentious, in particular, those related to the delivery methods, with concern raised over the possibility of experiments with smoked cannabis. A civil servant, Mr Stotesbury wrote,

Some of the research is likely to involve the smoking of cannabis by humans... in controlled conditions. The Misuse of Drugs Act 1971 and the Regulations enable the Secretary of State to approve premises for cannabis smoking... for research proposed and we may in due course be making recommendations for the exercise of this power. This could occasion some public interest.²⁷

Carrying out research on smoked cannabis was contentious on two grounds. First, it was too close to recreational use methodology and second, it was in conflict with the anti-smoking campaigns.

The report was not published. Correspondence within the Home Office in 1974 revealed concerns that calls for research might indicate to the public that calls for decriminalization were being considered. A civil servant commented,

*I am glad that you do not wish to publish this report. I regard it as important that it is neither published nor leaked. A casual reader would infer from it that the whole question of whether the law against the misuse of cannabis should be relaxed was under consideration. It would be unfortunate if this got about, particularly in the present political climate.... it may be necessary to consider the possibility of making public the commissioning of further research. Whether or how this might be done will need to be considered against the climate of the time.*²⁸

Nevertheless, the recommendations were important in the process of re-medicalization because they provided pressure to research cannabis to facilitate a clearer scientific base on which to formulate control measures. Arrangements were made for a further research sub-committee of the Interdepartmental Co-ordinating Committee to study the recommendations and to take steps to effect them through the appropriate research council or by direct application to the Home Office or DHSS.²⁹

After submission of the first interim report, the Working Group on Cannabis considered its next move. The original terms of reference had included other psychedelic drugs but it was decided that the focus should remain on cannabis. Topics of discussion included, how to obtain data on cannabis users, data on stop and search, and the effect of control measures, for example, the impact of legal charges on students' careers, and the effectiveness and impact of statutory controls.³⁰

Therapeutic use entered discussion to a greater degree this time and the balance in the risk-benefit analysis began to shift. Graham raised again the issue of therapeutic cannabis and took quite a different view to the stance taken by Edwards in the previous discussions. Graham argued that cannabis' potential as a medicine outweighed any

risks. He presented a paper in 1975 to the working group on the therapeutic potential of cannabis. In it he provided a brief history of cannabis use and highlighted its modern potential as a sedative, analgesic, appetite stimulant, immunosuppressive and its role in reducing intraocular pressure. Citing his own work at Cardiff, he drew attention to the potential uses of cannabis in asthma and for cancer patients.

*Cannabis or more probably some derivative should find a place as an adjuvant to established drugs: e.g. by inhalation when its action on the bronchial smooth muscle differs from that of isoprenaline or as an anodyne in the management of terminal carcinoma.*³¹

How its potential would best be exploited remained uncertain, though Graham appeared to favour derivatives over herbal cannabis.

However the Working Group on Cannabis' focus was on control measures. Throughout the 1960s and early 1970s cannabis use had increased despite increased controls and the apparent failure of the criminal justice system to deter cannabis use and the increased number of prosecutions, namely of young people, brought drug policy into question. The concept of decriminalization, the idea of maintaining prohibition but reducing or removing penalties, was gaining ground. The harms of cannabis had taken on a new meaning – not the pharmacological impact on the body but rather the social impact of controls and the creation of a black market. The aim of drug policy was queried in the working group - was eradication still a possibility, or was the emphasis moving to discouraging new cases and influencing prevalence of use?³² On this point, the effectiveness of the current system, division in the group intensified. Edwards expressed his general satisfaction with current laws. Searchfield reiterated his concern over the policy of fines and he drew attention to the fact that the concept of decriminalization was finding support despite the prohibitive moves of the international agencies.³³ There could be no unanimity. The second interim report of 1975 considered the effectiveness of statutory controls and their impact at large and on the lives of individuals. It recommended that there should not be any changes to the law in the light of uncertainty over long-term clinical and social effects of the drug, but it was accompanied by a minority report by Searchfield which favoured liberalization.³⁴ There

were no recommendations in relation to medical cannabis for the focus remained on the penal approach to drug control.

At a meeting on the 19th December 1975 the ACMD considered and eventually endorsed the second interim report, but expressed disappointment about the absence of proposals for further action. It was endorsed only in the expectation that the working group would reconvene within twelve months to continue its work and yield more productive results.³⁵ The issue of penalties was referred to other discussions on the penal system in connection with a study of maximum sentences. The report was submitted to Ministers but it was not published. The Home Office remained wary of re-opening public debate or of risking the report becoming incorporated with calls for legalization.³⁶

The report was not allowed to fade away quietly however. Leaks had plagued the discussions, channeling private closed discussions into the public domain. Information about a debate over a loophole in the law relating to cannabis leaves and the stark divisions within the working group were leaked to the *Guardian* and to the *New Scientist*.³⁷ The report was leaked also to Release, a drug voluntary organization set up in 1967 to advise drug users on the law. There were fears within government and the ACMD that Release planned to publish an article and quote from the report.³⁸ The issue of leaks featured prominently in the discussions during 1976. Searchfield who in private correspondence was deemed responsible for the leaks argued in favour of publication on the grounds that, '*interest reflects the public interest and suggests that it was better to seek publication from the outset in order to deflect criticism*'.³⁹ Graham perceived the public interest in cannabis had diminished and that therefore there was reduced political sensitivity. For Graham this made it the appropriate time to discuss the issue, though in his opinion publication was only worthwhile if the working group drew conclusions. Others like Mr PA Myers, Chief Constable of the North Wales Constabulary were afraid of re-igniting the controversy. Turner focused on the role of an expert group to advise, not to court public opinion. Edwards was against publication generally.⁴⁰ Concerns were raised, not merely with the leaks but, that they were targeted at an organization associated with legalization. Mr GI de Deney of the Home Office Drugs Branch linked the leaks to Searchfield.

Release is an organization which does a lot of good work. But it argues for legalization.... Alarming the second interim report should have found its way to this organization... Suspicion must, I'm afraid attach fairly strongly to Mr. Searchfield.⁴¹

The ACMD remained against publication citing the fact that the report was an interim report, not a final one, and that the cost of publication was an issue especially in the light of limited conclusions.⁴² The report was never published and the working group did not reconvene again until 1977 after requests from the government for advice over potential amendments to the Misuse of Drugs Act of 1971.

The Advisory Council on the Misuse of Drugs' Working Group on Cannabis and amendments to the Misuse of Drugs Act, 1977-1979

The Working Group on Cannabis was re-convened in 1977 with the express purpose of advising on potential changes to the Misuse Use of Drugs Act 1971 through amendments to a Criminal Law bill. The amendments which if adopted would have removed from the Misuse of Drugs Act the power of the courts to impose custodial sentences on summary conviction for unlawful possession of cannabis and, in essence, would have implemented a major recommendation of the earlier Wootton Report.

⁴³ When the bill was proposed ministers sought the advice of ACMD which advised a delay pending the ACMD's re-evaluation of the general principles which governed control of drugs and the application of those principles to various offences around controlled drugs.⁴⁴ Their actions were constrained, as the UK was signed up to the UN conventions and was obliged to prohibit non-medical use but there was some leeway within the control framework. The placement of cannabis in Class B or Class C of Schedule 2 of the Misuse of Drugs Act 1971, as opposed to legalization was the question. Three ACMD sub-committees were asked to consider the question. The Technical Working Group considered scheduling in relation to the pharmacological properties of cannabis and harm when misused, and was chaired by Graham. Another working group considered legal and administrative matters, and the Working Group on Cannabis, chaired by Bloomfield, considered the question of scheduling more broadly. In 1979, the ACMD on the advice of its working groups published its decision: that

cannabis and cannabis resin should be downgraded and re-classified from Class B to Class C and from Schedule 1 of the Regulations to Schedule 2. The recommendation to Ministers by ACMD was not based, however, on unequivocal advice from the working groups.

Behind the ‘performance’ of an expert committee, which may appear to present a united decision, can lie division and bitter arguments between members. A follow-up report by the ACMD in the 1980s summarized the conflicts:

Some members’ appraisal of all the available scientific evidence so far leads them to conclude that some alleviation of the penalties for unlawful possession could be contemplated at the present time without undue concern... others having regard to reports of current.... inconclusive scientific investigation are not satisfied that enough is known to make recommendations which would widely be regarded as implying that the risks of using cannabis and cannabis resin are less serious than was believed.⁴⁵

Scientific uncertainty meant that evidence was open to interpretation by individuals representing different professions and who placed different emphasis on the available evidence. Divisions intensified when the working group on cannabis could no longer prevaricate as it had in the period 1972-1976 and was instead required to make recommendations in relation to Criminal Law bill.

Divisions were clearly demonstrated in the interpretation of harms of cannabis use and their relationship to policy. For a meeting of the Working Group on Cannabis in 1977, Graham had prepared a paper on the long-term effects of cannabis on health.⁴⁶ As in 1972, he raised the issues of possible harms including foetal abnormalities, brain damage and mental health, but he drew out doubts over the validity of the data that led to these concerns and questioned their significance.

Anti-pot scientists interpret findings on cytotoxicity as indicating potential for damage. Then extrapolate from the laboratory to the sociological field and ignore the gross discrepancies between the concentrations of the drugin the laboratory to human science and advocate a ban. The cautious attitude is expedient, but I believe it is ill-founded.⁴⁷

Graham himself thought the research was problematic on harms and referred to Edwards on this matter.⁴⁸ But Graham was also chair of the Technical Sub-Committee and in its meetings he had called for a reconsideration of cannabis and questioned why cannabinal and its derivatives had been classified differently. The explanation was offered that it was to discourage the illicit manufacture of synthetic cannabis, a transfer in interest which Paton had earlier feared. Graham called for the transfer of derivatives to the less restrictive schedules.⁴⁹ With the harms of cannabis being brought into doubt so was the law and he brought these understanding to the Working Group on Cannabis. On these grounds the Working Group on Cannabis decided to recommend that cannabis be downgraded.

*The Criminal Law bill should be amended so as to provide that the penalties on summary conviction of simple possession involving any Class C drug should be subject to the condition that imprisonment could only be imposed in respect of second and subsequent convictions. In due course cannabis and cannabis resin should be transferred from Class B to Class C in order that offences of simple possession of those drugs could attract the revised penalties.*⁵⁰

This was a major development and instead of maintaining the status quo as had previously been the case, had the working groups' recommendations been accepted by government, it would have resulted in changes to policy.

However, this initial decision was challenged. Edwards who placed more emphasis on potential harms, was not prepared to accept downgrading. Edwards had been absent at the meeting in which the decision to recommend downgrading had been agreed. In later correspondence with the chair, Edwards expressed the view that he could not support the working group's decision.

*I would not myself have felt able to support those recommendations and was rather surprised to hear that the recommendations seem to have been made in the light of an impression that there is no evidence that cannabis can damage health.my own beliefs that the scientific evidence which has been accumulating over the last few years goes rather in the direction of suggesting that cannabis may well be a much more dangerous substance than that had previously been supposed.*⁵¹

Bloomfield, the chair, was forced on the defensive and he placed emphasis on the significance of Graham's report for influencing the decision to recommend the downgrading of cannabis. He wrote to Edwards,

*I think it is fair to say that one of the factors which influenced the group in coming to the conclusion it did was the report prepared by Graham on a review of the literature.*⁵²

At the following meeting, Edwards expressed his strong disapproval of the decision and re-iterated his view that cannabis was a threat to society. It also emerged that the Legal and Administrative Working Group had disagreed with the decision preferring the maintenance of the status quo. In Edward's view the uncertainty over harms necessitated the retention of the precautionary principle and justified the maintenance of the legal status quo. In a statement that illustrates how different professional standpoints can influence the end advice of expert committees, Edwards, argued that Graham's approach to the problem differed from his own in that Graham came from a pharmacological background whereas his own approach was epidemiological. Edwards expressed his concern with the sheer scale of the drugs problem and the effects over the long-term. He questioned Graham's use of evidence, and pointed out that Graham was open about this in his book, *Cannabis Now*, but not in the paper presented to the working group.⁵³ Edwards argued that their decision should not be based '*on proving harm, but the possibility of harm.*'⁵⁴ Edwards suggested a further subgroup and more research to resolve the issue. But the tide was turning against more delays. Graham argued for a more pragmatic approach, and pressed for immediate action rather than the status quo. The chair recognized that there was little chance of agreement and was against the creation of another sub-group.

*It is unlikely that a consensus would ever be reached and they were further restricted by time constraints since the Criminal Law bill would go to the House of Commons for the second reading in mid April.*⁵⁵

Bloomfield appeared to have reservations about the initial decision but denied that legalization had been contemplated. Edwards changed the discourse, and moved the discussion away from the potential harms of the impact of the criminal justice system

and back to the harms of cannabis use. Bloomfield dissented from the decision of the previous meeting, and argued that the law protected first offenders from imprisonment and therefore there was no good reason to change the penalties. He argued additionally that problems might arise from public misunderstandings if changes to policy were suggested and commented, *‘such an action might in the eyes of the public merely have the effect of devaluing the seriousness of misuse of the drug’*.⁵⁶ Searchfield was perplexed by the reaction of Edwards and Bloomfield to the cautious recommendation. Graham supported Searchfield though for different reasons commenting,

*It was merely a question of attitudes. If one was paternalistic, which he was not, then one felt justified in stopping people harming themselves.*⁵⁷

It appears that with inconclusive scientific evidence decisions depended less upon evidence relating to the potential harm of cannabis but more upon individual attitudes not only towards cannabis but to the role of science and government in society and depended greatly upon the personality and influence of those expounding a viewpoint on any particular day.

These arguments continued into the joint meetings of the three working groups. The Technical Sub Committee which had examined the classification of drugs under the 1971 UN Convention in relation to the pharmacological properties of drugs and their harmfulness when misused concluded:

*There is no compelling evidence that occasional moderate use of cannabis is likely to have detrimental physical effects on individual users....we concluded that the ...relation between chronic use of cannabis and mental impairment was by no means proven and that there appeared too many compounding factors involved.*⁵⁸

Graham’s opinion that *‘moderate smoking is not likely to damage the brain or destroy the personality of the smoker’* seemed to be taking hold in policy discussion of the pharmacological evidence of cannabis’s harm. The matter was somewhat different when social interpretations were introduced. The other two working groups had considered the evidence in relation to wider general principles and when the groups

came together the debate became more heated. Various options were discussed at the joint meeting of the three sub-committees: A separate class for cannabis; reclassifying cannabis as Class C; reclassifying cannabis as Class C and reducing penalties; or a reduction in all penalties.

Edwards outlined three benefits of downgrading cannabis. One it would mean the law was less draconian, it would provide an educative effect by removing the mystique around cannabis and third it would make the letter of law compatible with its implementation. But in light of the disadvantages he remained against the amendment. The question was put to a vote, which marginally came out in favour of downgrading.⁵⁹ In the end, cannabis was split into its constituent parts. The sub-committees concluded that THC was a dangerous substance and there were no recommendations to remove this from Class A. This was not the case with herbal cannabis as evidence of harm remained inconclusive and a majority decision recommended reclassification of cannabis and cannabis resin from Class B to Class C.⁶⁰

Once the sub-committees had decided to recommend downgrading cannabis, the practicalities of carrying this out raised problems. As far as Edwards was concerned cutting penalties for possession, but not on supply, was illogical and he retained the view that the law had a part to play in educating people to realise that the use of all chemicals carried risks and therefore it would be best to leave the law as it stood. Graham argued that this was not the role of the criminal justice system and the minutes of 1978 recorded his comments.

*Whilst he supported Edward's idea that there should be an education effort to discourage cannabis use he did not agree that the educative function of the law warranted retention of heavy penalties in the absence of further evidence.*⁶¹

The debate was going round in circles and the secretary was forced to intercede and remind members that they had accepted a decision to recommend the reclassification of cannabis to Class C. The final report of the ACMD argued that it was best to concentrate on limiting supply. The ACMD report argued that the use of these drugs should not be legalized and that a deterrent was still needed, but that cannabis should

be transferred from Class B to Class C and that the penalty of imprisonment on summary conviction for unlawful possession of all drugs in Class C should no longer be available.⁶²

Merlyn Rees, the Home Secretary, rejected the advice of the ACMD to downgrade cannabis. Dr Hardwick of the Ministry of Health wrote to members of the ACMD justifying this rejection not on scientific grounds but on the need to retain the deterrent effect.

*...The decision was taken both on grounds of principle and on practical grounds. The Home Secretary considers that any relaxation in control could be taken to mean that the health risks from using cannabis had been exaggerated, thus encouraging its use.*⁶³

Florin has argued that uncertainty comes in two forms, technical and social.⁶⁴ When accepting or rejecting the advice of its experts government may act on more than scientific or technical knowledge, by taking into account social considerations. As Florin wrote, '*social uncertainty..... not entirely solved by scientific evidence. Its resolution depends on political and other institutional interventions.*' She argued that in a study of general practice contracts that they were neither evidence-based nor evidence-free. Scientific factors interacted with social, political, and professional interests." This, Florin argued, takes value judgments rather than technical assessment. In the case of cannabis policy, rational decision-making was at risk at two points: in the production of that expert advice and in the uptake or avoidance of that advice.

The report generated a degree of public interest and the Legalise Cannabis Campaign quickly published *Trash Rehashed* which criticized the ACMD on many grounds including: not going far enough in making recommendations concerning the law, the long time span of the review, the poor quality of the report and they emphasized the divisions within the committee.⁶⁵ Legalization was never on the agenda though and a note from a civil servant in 1979 indicated the views within the Home Office, '*I would not go to the stake to prevent cannabis being classified C instead of B. I can see no real advantage to this move which would doubtless be misinterpreted. I would resist*

*legalizing cannabis strongly. I doubt if the Home Office will do anything which will upset DHSS ministers.*⁶⁶ *Trash Rehashed* had also raised the issue of access to cannabis for medical purposes on prescription, and whilst the points on legalization were dismissed further advice was sought on this point and the issue of therapeutic cannabis was raised later as a specific point in subsequent discussions.⁶⁷

The ACMD had provided an arena for discussion around cannabis to take place and allowed a more positive viewpoint from a pharmacological standpoint to influence debate over policy. Uncertainty, not only over understandings of cannabis, but what to do with the ‘evidence’, allowed scope for subjective decision-making within the working group and for government decisions on whether to take or ignore the advice. However, the process created a slightly more flexible and relaxed attitude towards cannabis within the policy network. It was this combination of more relaxed attitudes towards cannabis, research incentives, as well as a developing need to draw medical needs away from discussion of drug control, that was to allow the process of re-medicalization to develop in the following decades.

The Advisory Council on the Misuse of Drugs and the Expert Group on the Effects of Cannabis, 1980-1982

The Expert Group on the Effects of Cannabis was established when the ACMD wanted to look again at the control of cannabis and cannabis resin under the Misuse of Drugs Act 1971 and required advice from scientists before it decided to what extent cannabis should be controlled *‘Further evidence on all aspects of cannabis action continued to become available causing the Council to decide to establish an expert group to assist the Council in its consideration of the implications for future official policy on the use of cannabis and cannabis resin.*⁶⁸ The previous working groups had opened up debates over the possible harms of cannabis and Griffith Edwards requested a separate group to look at the adverse effects of cannabis and he attempted to influence the group’s composition and recommended that Paton be brought into the group.

I actually made the suggestion that we needed a working group specially to look the damage questions and I persuaded the Council to ask Bill Paton

*to join use, because for some extraordinary reason he was never a member of that Council. We produced a report which I think was objective on the possible harms and many open questions.*⁶⁹

However, this time the expert group was chaired by JDP Graham, who had consistently questioned the harms associated with cannabis use, and brought research on the therapeutic use of cannabis to the attention of the working group throughout the 1970s. He continued to bring the issue of therapeutic cannabis to a more prominent position in discussions of the 1980s. This expert group included many members of the original Working Group on Cannabis, including, J Bloomfield, the previous Chair, and Griffith Edwards. Other members included, Professor W Cranston from St Thomas' Hospital; Dr B Hunt from the Department of Health and Social Security, Dr McNicol, Principal and Vice Chancellor of the University of Aberdeen; Mr D Turner, from St Barts Hospital; Dr B Saunders, and Dr Harvey from Department of Pharmacology Oxford, and Sir William Paton.⁷⁰

The ACMD indicated that the expert group should look anew at the question of cannabis controls, and that it should “disabuse itself” of past considerations and recommendations. Under pressure from developments at home and abroad, the remit described the political background. It noted the government’s obligations under the 1961 UN Convention to limit the use of cannabis to legitimate medical and research purposes but the government was also facing the demand of a small but articulate section of the population for legalization and there was also pressure from some members of the UN to remove cannabis from the most restrictive categories. The task of the expert group was to assist the ACMD in forming a view of cannabis controls on the basis of scientific findings.

For the first time the issue of the medical use of cannabis was specifically raised in the remit of the expert group.

*The group should bear in mind that the constraints placed on a drug by the MDA related to its social use and misuse if the appropriate bodies decided that cannabis had value as a therapeutic agent it would be possible to amend the regulation to authorize doctors to use cannabis in this way.*⁷¹

The increased interest in therapeutic use by the 1980s had filtered more centrally into discussions of the expert group. The key issue was the developing use of cannabis for specific ailments most notably in the alleviation of symptoms caused by the chemotherapeutic treatment of cancer.⁷² The movement of cannabis into the clinical environment did not proceed without attracting controversy and concern. Any blurring of the boundary between recreational use and calls for legalization and medical applications was of particular concern, for example, as discussed in the previous chapter over the case Dr Rose.⁷³ It was viewed as more risky to prohibit access in certain circumstance as it was assumed that there was sympathy in the wider community for such research and this outweighed fears over any message of encouragement it might provoke for legalization. The Advisory Committee on the Misuse of Drugs set up an expert sub-committee in April 1980 to evaluate the science on the therapeutic use of cannabis. The social use of cannabis was not within the sub-committees agenda though it did consider toxicity.⁷⁴ Attitudes too were altering in the international arena. The WHO by the 1980s had begun to move away from its previous stance that cannabis medicine was obsolete towards a cautious acceptance of cannabis' medical utility. Meetings and reports of the WHO, such as the joint report with the Addiction Research Foundation of Ontario in 1981 looked at cannabis and its problems but downplayed the threat of cannabis use.⁷⁵ In the UK, whilst the earlier advisory committees had discussed the relative benefits or harms of therapeutic aspects of cannabis, by the 1980s the focus shifted to the technical issues surrounding such research.⁷⁶

By this time there was interest in the DHSS on the potential therapeutic uses of cannabis and it was against this background that a paper prepared by Dr B Hunt of the DHSS was presented on the therapeutic use of cannabis to the expert group. Dr Hunt highlighted the many avenues that had been investigated for cannabis and re-iterated that the most promising application was as an anti-emetic for patients undergoing cancer chemotherapy.⁷⁷ The debate had moved on from one focused on the advisability of cannabis-based medicine to one focused on safety and efficacy for patients.

*The efficacy of cannabis as an anti-emetic was undeniable, but it could be questioned whether its efficacy outweighed its toxicity. It could only be used for certain patients in certain circumstances.*⁷⁸

But the dangers were not viewed as being so great, as to discourage research, even on additional applications. Hunt went on to comment,

Great claims had been made for it treating glaucoma but a thorough topical examination of these claims was needed. The use of the drug for epilepsy and asthma was interesting particularly the use of CBD in treating epilepsy but again more work needed to be done. The evidence for the use of cannabis as an analgesic was extremely equivocal, but it was certainly worth looking at.⁷⁹

The expert group heard papers presented on a variety of other topics including the issue of cannabis dependence by Edwards; kinetic and metabolic information on cannabis and related compounds by Turner; the effect of cannabis on the lungs and respiratory system by Cranston; the effects of derivatives on cell division by McNicol; and cerebral damage in man and animals, by Corsellis Driver and Lantos; and cardio-vascular effects were described by Paton. The final report of the Expert Group on the Effects of Cannabis were of significant interest for the re-medicalization of cannabis. First, the Report placed the burden of proof on proving the harmful effects of cannabis which it argued had not been fully demonstrated.

There is insufficient evidence to reach any intestable conclusions on the effect of cannabis on the human body, it affirmed that research undertaken so far failed to demonstrate positive and significant harmful effects on man solely due to the use of cannabis, and that areas where evidence suggested deleterious effects needed further research.⁸⁰

It queried some of the key concerns over the use of cannabis therapeutics and in so doing helped open the way for further research in later decades.

Second, the issue of therapeutics had become important enough to warrant specific discussion and recommendations instead, as had previously been the case, a sideline to the legal and social discussion. Importantly, the report acknowledged that scientific study had endorsed anecdotal reports of cannabis' medical applications and indicated a need for further research.

Many traditional therapeutic uses of cannabis have been confirmed by scientific research, but in most instances to date with no greater efficacy than existing modern drugs. Its use as an anti-emetic in cancer chemotherapy appears to be most promising and other possible therapeutic uses are in relation to glaucoma, epilepsy and muscle spasticity, but much more research is required before its use in any of these areas can be accepted as a standard method of treatment.⁸¹

The Hunt paper indicated the need for more research on nabilone.⁸² These conclusions provided some degree of legitimacy for therapeutic cannabis as an independent area of research instead of linking it to disreputable recreational use within the drug control framework. The report considered how potential cannabis-based medicines could be made available.

If the appropriate bodies decided that cannabis had value as a therapeutic agent it would be possible to amend the regulations to allow doctors to use cannabis in this way.⁸³

The Regulations allowed for amendments to the Misuse of Drugs Act of 1971 and it was possible that cannabis could be shifted from Schedule 1 to Schedule 2 of the Regulations which would have allowed research and medical uses. Work in the laboratory and the clinic was deemed sufficiently promising to justify further investigation and the report provided support for further research into cannabis' therapeutics by concluding that there was evidence *'to suggest that the therapeutic use of cannabis on certain medical conditions may after further research prove beneficial'.⁸⁴*

The expert group recommended the downgrading of cannabis from Class B to Class C. and as it had in 1979 it reiterated the view that the penalty of imprisonment on summary conviction for unlawful possession of cannabis should be removed.⁸⁵ Once again its advice was rejected by government, and again not on the evidence but rather the message that downgrading might portray. DJ Hardwick, of the Home Office wrote to members of the ACMD on the 16th March 1982 to explain the decision.

...The Home Secretary has after careful consideration decided not to implement the recommendation of the Council for changes in the law relating to cannabis...the decision has been taken both on grounds of

*principle and on practical grounds. The Home Secretary considers that any relaxation in control could be taken to mean that the health risks from using cannabis had been exaggerated, thus encouraging its use.*⁸⁶

Fear remained over the potential ‘misunderstanding’ of the report and a draft press release deleted the sentence ‘*much of the research has failed to demonstrate the positive and significant harmful effects in man attributed solely to the use of cannabis.*’ It did refer however, to the evidence that suggested that the therapeutic use of cannabis or substances derived from it ‘*may after further research prove beneficial.*’⁸⁷

Despite the rejection of the report by government the discussions of the ACMD reflected a changing understanding of cannabis. Penalties for cannabis offences were reduced and in the 1980s there was a greater focus on cautioning and small on-the-spot fines, rather than imprisonment. By the 1980s, attitudes towards cannabis as a medicine began to shift from hostility to one of cautious encouragement of research. The Report of the Expert Group on the Effects of Cannabis Use downplayed the dangers of cannabis, and put weight behind the possible medical benefits of cannabis.⁸⁸ It had allowed initial attempts at separating discussion of cannabis therapeutics from the misuse of drugs, and altered the environment around cannabis to one more receptive to the re-medicalization of cannabis. Few contested cannabis’s potential value for medical applications, where current licit medicines were not effective. At this stage in the process of re-medicalization of cannabis the quality of the evidence surrounding cannabis was inconsistent, and often contradictory. Calls for further research were a necessary step and shifted the discourse onto overcoming practical hindrances to further research including cost, and the limitations of supply. In 1982 a meeting on the therapeutic use of cannabis was arranged to discuss matters related to therapeutic use and to clarify where, within the DHSS, responsibility for policy on therapeutic cannabis should lie. Dr Wrighton, of the MRC argued that if increased use of more powerful cytotoxic drugs continued then cannabis would become of more interest to UK researchers. The law was not seen as a deterrent to research rather it was the cost and supply of THC, which no UK firm was prepared to synthesize, that was the problem. Furthermore, a product licence for manufacture had to be obtained but could not be granted prior to the Committee on Safety of Medicines being satisfied with

safety. This meant clinical research had to be repeated in the UK before cannabis-based medicines could be made available. To facilitate this, it was agreed that attempts should be made to encourage researchers to apply to the MRC with protocols, including the costs of THC. A split between medical use and misuse was also encouraged within the Department, as due to the use of cannabis in relation to cancer chemotherapy it was agreed that policy should *'properly rest with HS1 and MED SEB. It was agreed desirable that responsibility should not rest with MED MHI or SHO in view of their concern for the misuse of drugs.'*⁸⁹ It was recommended that further work should be carried to identify the structure and specification of the effective components in cannabis. But interest in cannabis both in research and policy circles had shifted away to other drugs of misuse. When interest revived with the breakthrough in the mode of action, research, which up to this point had been driven primarily by an interest in the misuse of cannabis, became driven by a greater interest in the therapeutic use of cannabis.

Conclusion

The development of the mechanism for science-policy exchange allowed formal discussion of cannabis and the potential of therapeutic cannabis to filter through to policy circles. When formulized statutory expert groups began discussing drug control after 1973, cannabis was no longer regulated as a medical product. But cannabis functioned as a medical product in self-help circles for some patients and in the professional sphere, as a potential medicine in the laboratory and clinic. In this sense policy was running out of step with scientific developments and the issue of therapeutic cannabis was increasingly drawn into policy discussion providing a route for science-policy transfer. Drug policy and cannabis was discussed within the confines of the UN Conventions, but as a boundary substance and one slowly being re-drawn towards medical regulation, any discussion of cannabis as a drug of misuse and its place within the criminal justice system had to include discussion of emerging therapeutic applications. In this context discussions saw a change in focus over the period 1972-1982. Initially, between 1972-1976 expert discussion on cannabis began as an exercise in information gathering, with initial interest in understanding the state of cannabis

research, the use of cannabis and the effects of control measures which were in flux. Discussions drew out the paucity of the knowledge base on which to ground policy and added pressure for research. Whilst reference was made to therapeutic cannabis the main impact was to encourage cannabis research which would later indirectly lead to therapeutic applications. Whilst government was looking for expert advice, expert advice was guided by existent evidence, however up to and during this period the evidence was not clear cut and to some degree it became an issue of interpretation. Division amongst members emerged and resulted in no clear conclusions being drawn, instead further research and the status quo over the law was recommended. Between 1977-1979 a change was discernable. Though discussion of cannabis became increasingly acrimonious, in general the dangers of cannabis were played down, and eventually the working group and the ACMD decided to recommend downgrading of cannabis from Class B-C. Whilst the recommendations were ultimately rejected by the government cannabis harms were called into question and the working group, when left with no option but to make clear conclusions for the Criminal Law bill, adopted a more relaxed attitude to cannabis. The period 1980-1982 saw a further alteration in focus with discussion becoming less heated and less focused on cannabis harms, and conclusions backed up the previous recommendation to downgrade cannabis. Specific discussion on therapeutic use emerged and research into therapeutic applications rather than research into cannabis generally was encouraged. With cannabis derivatives entering the clinic and by 1982 medical drug regulation, therapeutic cannabis was accepted as a potential reality and discussion focused less on the wisdom of using it as a medicine but rather on the cost and practicality of doing so. Recommendations to downgrade cannabis were again rejected by government and there were no changes in respect to scheduling but penalties were in essence reduced. But the public health needs of cannabis as a therapeutic were more influential in driving discussion. In this period the issue of therapeutic cannabis was not yet disassociated from discussion of recreational use and control measures as it would become to a degree in the 1990s. When by the end of the 1980s a breakthrough in the mode of understanding of cannabis emerged, cannabis as a medicine would become treated as a topic in its own right, and the door was open to provide justification to split cannabis as a medicine from discussion over the control of recreational cannabis use. Practical hindrances

to cannabis research would be considered by therapeutic specific, independent public committees that emerged in the 1990s, which paved the way for clinical trials and UK industrial involvement with medical cannabis.

¹ Berridge, *Marketing Health*.

² Ibid.

³ See appendix 7 for a list of expert committees.

⁴ Ministry of Health Scottish Home and Health Department, *Drug Addiction (The Brain Report)* (London: HMSO, 1961).

⁵ World Health Organisation (WHO) *Third Report. Expert Committee on Drugs Liable to Produce Addiction*, 57 (Geneva: WHO, 1952).

⁶ Ministry of Health Scottish Home and Health Department, *Drug Addiction: The second report of the Interdepartmental committee on drug addiction* (London: HMSO, 1965).

⁷ Home Office, ACMD Terms of Reference, <http://drugs.homeoffice.gov.uk/organisation-search/UK-and-National/acmde42d.html?version=1>

⁸ G. Edwards, speaking in a witness seminar and the re-medicalization of cannabis in S.M. Crowther, L. Reynolds and T. Tansey, *The Medicalization of Cannabis*.

⁹ Ibid.

¹⁰ Berridge, *Marketing Health*, p. 134.

¹¹ G Stimson, and R Lart, 'The relationship between the State and the Local Practice and the Development of National Policy on Drugs Between 1920 and 1990' in Strang and Gossop, *Heroin*, p.181

¹² T.L.B. Spriggs, 'JDP Graham, Obituary,' *British Journal of Pharmacology*, 99(1) (1990), pp. 3–4.

¹³ G. Edwards, speaking in a witness seminar and the re-medicalization of cannabis in S.M. Crowther, L. Reynolds and T. Tansey, *The Medicalization of Cannabis*.

¹⁴ TNA, Home Office papers, HO 319/162, Minutes of the 1st meeting of the working group on cannabis, 1st of December 1972,

¹⁵ TNA, Home Office papers, HO 319/165, minutes of the 4th meeting of the Cannabis Working Group, 13th of July 1973.

¹⁶ TNA, Home Office papers HO 319/166 paper by Griffith Edwards, Cannabis and the criteria for legislation of a currently prohibited recreational drug: Groundwork for a debate.

¹⁷ TNA, Home Office papers, HO 319/166, Minutes of the 5th Meeting of the Cannabis Working Group, 19th September 1973.

¹⁸ TNA, Home Office papers, HO 319/175, Minutes of the, 5th Meeting of the Cannabis Working Group, 22 October 1975.

¹⁹ Ibid.

²⁰ TNA, Home Office papers, HO 319/166, biochemical and pharmacological studies. TNA Home Office papers, HO 319/164, Minutes of the 3rd meeting of the Working Group on Cannabis, 23rd May 1973

²¹ TNA, Home Office papers, HO 319/166, Minutes of the 5th meeting, Working Group on Cannabis, 19th September 1973.

²² Ibid.

²³ Ibid.

- ²⁴ TNA, Home Office papers, HO 319/167 ACMD Working Group on Cannabis First Interim Report, 1973.
- ²⁵ Ibid., Attachment to first interim report of the Working Group on Cannabis, Bloomfield December 1973.
- ²⁶ S. Jasanoff, *The Fifth Branch: Science Advisers as Policymakers* (Cambridge, MA.: Harvard University Press, 1990).
- ²⁷ TNA, Home Office, HO 319/167, Mr Stotesbury, Probation and After Care Department, 3rd January 1974, Advisory Council on the Misuse of Drugs Working Group on Cannabis First Interim Report.
- ²⁸ TNA, Home Office papers, HO 319/ 167, Letter from Mr TD McCaffrey, Public Relations Branch, to Mr Stotesbury 14th of January 1974.
- ²⁹ TNA, Home Office papers Ho 319 167 Advisory Council on the Misuse of Drug Working Group on Cannabis.
- ³⁰ TNA, Home Office papers HO 319/144, Minutes of 9th Meeting of the Working Group on Cannabis, 27th of March, 1974; TNA, Home Office papers HO 319 170 minutes of the 11th meeting of the Working Group on Cannabis 27th September 1974.
- ³¹ TNA, Home Office papers, HO 319/172, Minutes of the 13th Meeting 9 July 1975, paper presented to the working group by JDP Graham, Therapeutic Possibilities in Cannabinoids.
- ³² TNA, Home Office papers HO 319/168 Minutes of 8th Meeting of the Working Group on Cannabis, 8 February 1974, item four, paper from the Home Office on the 'Effects of Statuary Controls on the Use of Cannabis.
- ³³ TNA, Home Office papers, 319/175, Minutes of 5th Meeting, of the Working Group on Cannabis, 22 October 1975.
- ³⁴ TNA, Home Office papers, HO 319/174, Reservation and Alternative Conclusions to the Second Interim Report.
- ³⁵ Ibid., Second Interim Report on Cannabis, Letter from GI de Deney Home Office to Mr Glanvill, 6th May 1976.
- ³⁶ TNA, Home Office papers HO 319/174 note from Mr DI de Denny Home Office.
- ³⁷ Ibid., press cuttings, Drug report Back into the Melting Pot 2/12/1976, and New Scientist. TNA, Home Office papers, HO 319/179, Minute of the 19th Meeting of the Working Group on Cannabis, 28th February 1977.
- ³⁸ Ibid., Advisory Council on the Misuse of Drugs Second Interim Report of the Working Group on cannabis. 4 .6 1976
- ³⁹ TNA, Home Office papers HO 319/177, Minutes of the Working Group on Cannabis, 26th November 1976
- ⁴⁰ Ibid.
- ⁴¹ TNA, Home Office papers, HO 319/174. Letter from de Deney to Mr Glanville, 6th of May 1976.
- ⁴² Ibid., ACMD response to Second Interim Report.
- ⁴³ TNA, Ministry of Health papers, MH 149/1946, Expert Group on the Effects of Cannabis report, 1982
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- ⁴⁵ Ibid.
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Chapter Five

Industrialising cannabis: The pharmaceutical industry and the re-medicalization of cannabis 1973-2001

The pharmaceutical industry has been crucial in the process of the re-medicalization of cannabis and this chapter charts the gradually increasing interest of industry after the loss of cannabis tincture in 1973. This chapter overlaps slightly in time with other chapters but it provides an in-depth analysis of the role of pharmaceutical industry in the process of re-medicalization. It begins by describing the problems caused by a lack of industry interest pre-1973. In contrast, it then considers the importance of temporary industry involvement in the 1970s and 1980s which provided two boosts to re-medicalization. First, there was the development of compounds that never reached patients but were useful for scientific research, and second, the production of synthetic cannabinoids that entered the clinic and became licit, if unpopular, medicines. Then, from the 1990s, major scientific breakthroughs opened up two avenues of research and re-stimulated industry interest. One avenue was the investigation of drugs that could activate the newly discovered endocannabinoid receptor system; drugs that were not based on cannabis itself. The other avenue, and the one on which this chapter concentrates, was the investigation of extracts of cannabis. 1997 marked a new era when GW Pharmaceuticals, a small UK biotechnology company based solely on investigations into herbal cannabis, began cultivation of standardized cannabis plants for the production of cannabis-based medicine extracts (CBMEs) delivered via a new drug delivery system. The re-medicalization of cannabis is placed in the context of developments in the pharmaceutical industry and the rise of biotechnology; the interrelations between academic science and industry; the rise of phytomedicine, and the major scientific discovery of cannabis' mode of action via the endocannabinoid receptor system.

Cannabis in the laboratory: The pharmaceutical industry and cannabis prior to 1980

In the twentieth century the history of therapeutics was inseparable from the rise of the pharmaceutical industry. Historical and sociological research provide frameworks for investigating the role played by the pharmaceutical industry. Histories of pharmacy and the pharmaceutical industry divide its development into several stages: kitchen physic or home remedies; the rise of commercial remedies often mixtures of secret ingredients; development of pathology and microbiology; growth of multinational pharmaceutical companies, acquisitions and mergers and the elimination of small-scale industry; and the emergence of small biotechnology companies.¹ These different stages of the pharmaceutical industry have been reflected in the process of the re-medicalization of cannabis. In the initial development of the pharmaceutical industry historians cite the importance of a greater understanding of vegetable and mineral substances used as medicines.² The isolation of an active principle was essential. Major discoveries included the isolation of morphine from opium, aspirin from willow bark, and later quinine from cinchona. In the late nineteenth and early twentieth century, when these discoveries were taking place, cannabis, was more of a commercial remedy than a pharmaceutical grade medicine, and as discussed in chapter two its active principle was not discovered until 1964, and synthesised in 1965. Cannabis missed the ‘cascade of medicine’ which took place during the ‘therapeutic revolution’ of the 1940s-1960s and which led to the expansion of the pharmaceutical industry worldwide.³ In the UK, the development of the NHS and its subsequent mass market for drugs stimulated a flurry of new drugs, such as cortisone, beta blockers and the contraceptive pill. Aside from technical problems cannabis remained unattractive to the pharmaceutical industry as a result of its increasingly prohibitive legal status.

This dearth of interest by a flourishing pharmaceutical industry had wider implications for the understanding of cannabis: it caused problems for academic research. Authors who have written about the pharmaceutical industry and pharmacy have highlighted the importance of accessibility to research material and how it can shape social and cognitive developments. This was shown in the development of

the Taxol drug from the yew tree. One of the major issues for research into cannabis pharmacology was the lack of a ready supply of the active principle, THC.⁴ Industry was not interested in producing THC or in the development of cannabis-based medicines. Mechoulam later explained how the legal status of cannabis deterred companies.

*Many of the major pharmaceutical companies.....had small groups working on cannabis. But as soon as it went up...the bureaucratic ladder... all ... decided not to go with cannabis because of the bad publicity. They were afraid of it....*⁵

Researchers at Oxford and at the MRC had unsuccessfully courted industry involvement in the early 1970s and the attraction of industry to the cannabis field remained a pre-requisite for the development of cannabis-based medicines and in the UK there remained an interest in the stimulation of domestic pharmaceutical industry involvement.

Fleeting pharmaceutical industry interest proved important. Reacting to reports in the 1970s that cannabis and THC suppressed pain in experimental models, an international pharmaceutical company, Pfizer, developed a synthetic cannabinoid compound, Levonantradol, an analogue of THC, as a potential analgesic and the related compound CP55,940. These compounds proved more water soluble than THC and so more useful for research purposes. Pilot clinical trials were carried out with Levonantradol in suppressing postoperative pain and in preventing the nausea and vomiting associated with cancer chemotherapy. However, unable to separate the beneficial clinical effects from the intoxicant effects, Pfizer abandoned the project by 1980.⁶ Throughout most of the 1960s and 1970s when interest in cannabis in academia was triggered, industry interest remained focused on alternative directions or showed only fleeting attention. The pharmaceutical industry itself was facing increasing restraints on its operations and undergoing a slowdown in development. Slinn explained the impact on the production of new drugs.

When that took place not only was the therapeutic revolution over, but increasing regulation to ensure product safety...was making the time

*between the discovery of a new compound and its launch...much lengthier, eating into patent life. The R& D process...was...becoming much more expensive.*⁷

However while the Pfizer compounds were abandoned as medical products, these compounds later provided a useful tool for academic cannabis research.

Cannabis in the clinic: The development of synthetic cannabis-based medicines, (CBMs) 1982-1987

The 1980s heralded a major new development in the process of re-medicalization of cannabis. Pharmaceutical industry involvement in the US built on the research into cannabis-based drug in the 1970s and two cannabis-based drugs made it out of the laboratory and into the clinic and through medicine licensing systems. The main interest from the pharmaceutical industry's perspective had been to find compounds that had the benefits of cannabis but without the psychoactive element. It was hoped that such products could circumvent the restrictive legislation around cannabis. Eli Lilly, had prepared cannabis preparations with standardized tincture of cannabis indica in the early 1980s and went on to develop nabilone, a synthetic cannabinoid, an analogue of THC. Whilst nabilone was not a naturally occurring cannabinoid it was pharmacologically very similar to phytoTHC. It was branded by Eli Lilly as Cesamet for prescription to cancer patients.⁸ With no other effective treatments for nausea caused by chemotherapy, nabilone was approved in 1982 for hospital-only prescription for 'nausea and vomiting caused by cytotoxic chemotherapy unresponsive to conventional anti-emetics' in the UK where it was not a controlled drug.⁹ Cesamet capsules for the treatment of nausea and vomiting associated with chemotherapy were licensed by the FDA in 1985.¹⁰ UNIMED, a newly established subsidiary of the Belgium based Solvay Pharmaceuticals, bought dronabinol, an isomer of THC, from the National Cancer Institute; part of NIH in order to bring the drug from research to market.¹¹ Dronabinol was given approval for the treatment of nausea in cancer chemotherapy in 1985 and dronabinol, in sesame oil, was marketed as Marinol. It was distributed by Roxanne Laboratories, an independent subsidiary of the German Boehringer Ingelheim Corporation by 1987 and later in 1992 its approval was extended in the US to cover

appetite loss related to AIDS in the US. Dronabinol (Marinol) was never licenced in the UK though it could be prescribed as an unlicensed drug on a named-patient basis. These were the first cannabis-based drugs introduced to market since the removal of cannabis tincture.

These licit medical drugs faced two problems. First, they proved unpopular with patients, and second medical derivatives of cannabis posed problems for the drug control agencies as they re-introduced a dual role for cannabis. In discussing the development of the 1971 Convention on Psychotropic Substance, McAllister demonstrates that the pharmaceutical industry argued for a cost-benefit analysis of psychotropic substance arguing that under medical supervision the benefits of psychotropic substances outweighed their risks and therefore warranted less stringent control measures.¹² These arguments did not seem to work for pharmaceutically produced derivatives of cannabis. The US Drug Enforcement Agency concluded that nabilone was too closely related to cannabis and gave it a Schedule II classification under the US Controlled Substances Act, signifying that it was considered a dangerous drug, although having some medical usefulness. With cannabis as the lead, nabilone was not far enough removed from its source. This classification placed rigorous restrictions on the use of the drug.¹³ Eli Lilly upset by the strict classification lost interest and never marketed it though it was used in the UK for clinical research.¹⁴ This was a major problem when the marketing of drugs proved crucial to their success or failure. It was also expensive and was discontinued in 1989.¹⁵ Dronabinol had been placed in Schedule I of the 1971 UN Convention on Psychotropic drugs and this placement proved problematic for its wide-scale use as a medicine product in the form of Marinol. In 1987, the US Government requested the UN to transfer dronabinol to Schedule II of the 1971 Convention and the WHO was requested to consider the matter. Recognizing some therapeutic benefit in certain instances but also the close relationship to the plant, it rated the abuse potential as 'high' but argued that dronabinol should be downgraded to Schedule II,

The abuse liability of dronabinol is high and its therapeutic usefulness as moderate to high...although few public health and social problems are currently associated with the therapeutic use of dronabinol, this substance is

*the active principle of cannabis and is capable of producing the same effects as the plant material.*¹⁶

The decision was not unanimous: two members of the WHO committee disagreed fearing that downgrading would send out the wrong message and would promote the abuse of cannabis and its extracts. Whilst the medical agencies were demonstrating a shift in attitude and were looking at cannabis medicines more favourably, drug control agencies were not. The Commission of Narcotic Drugs concurred with the minority view when it chose not to endorse the recommendation of the WHO committee and argued that cannabis' benefits did not outweigh its potential for abuse.

Since the drugs failed to live up to expectations the pharmaceutical industry interest in cannabis tailed off. In general there was a dwindling in the numbers of new drugs feeding through the pipeline. There were a number of reasons for this. Drug discovery had become based upon an understanding of the underlying mechanism of disease, a process which took much longer than the accidental discoveries of the past.¹⁷ The spiralling cost of healthcare, an ageing population, and the growth of chronic diseases encouraged governments to demand lower prices for pharmaceuticals which contributed to the restructuring of the pharmaceutical industry in the 1980s.¹⁸ The cannabis research field declined as researchers who had become involved in the 1960s shifted their research interests to emerging drugs like amphetamines, and cocaine, and funding on cannabinoids dried up.¹⁹ In such an environment cannabis-based medicine might have remained dormant but for major discoveries that revitalized the whole field.

Understanding cannabis' mode of action and the role of the pharmaceutical industry, 1988-1997

*After receptors were discovered.... cannabis became respectable... Lots of drug companies still worried about drugs that activate receptors so they looked at blocking them....for example for blocking appetite...there was lots of money to be made out of that.*²⁰

In the mid 1980s researchers questioned the lack of stereo-specificity of cannabinoids and began to hunt for specific receptors for the psychoactive cannabinoids in the brain.

By the late 1980s interdisciplinary international research between medicinal chemists and pharmacologists working on cannabis yielded results which led to a breakthrough in the understanding of the mechanism of action of cannabis thereby clarifying the way in which cannabinoids worked on the human body. This research re-opened the issue of cannabinoid receptors, and led to the discovery of what is now known as the endocannabinoid receptor system.²¹ The interdisciplinary approach was vital. Steve Hill a Professor of Molecular Pharmacology at Nottingham University highlighted the importance of the interdisciplinary approach to pharmacology and drug discovery.²²

The power of collaboration between chemistry and pharmacology is immense and the success of this alliance has underpinned astonishing successes in the development of powerful therapeutic drugs.²³

This interdisciplinary approach was particularly important in the process of the re-medicalization of cannabis.

Pertwee later expressed the importance of developments in pharmacology which provided an improved understanding of the mode of action of cannabis, for instance, signaling by G-protein-coupled receptors.²⁴ Chemical signalling is the primary means to control biological functions and the role of the receptor is to recognise these chemical signals. Receptors have been described as lying at the heart of pharmacology and were important in medicine.²⁵ Targeting receptors had become a focus for modern drug technology and therefore the emergence of research demonstrating that cannabis acted on receptors proved pivotal to cannabis' re-medicalization.

Developments within the pharmaceutical industry provided the tools which ensured that research on the cannabis receptors could take place. This was a classic example of how industry could influence academic research.²⁶ The cannabinoid compounds abandoned by Pfizer took on a new lease of life in academic circles. The Pfizer compounds proved to be a better tool than THC for researchers. Pertwee described later the importance of the compounds.

It was those compounds that led to the discovery of the receptor. THC although it does bind to the receptor is so fat soluble, it's very difficult to show that it binds. Can't actually use it as a probe.²⁷

By radio-labeling the Pfizer compound to act as a tracer, it was possible to detect the recognition sites of receptors.²⁸ It became almost certain that cannabinoids were specific in action and acted on a G-protein-coupled receptor, overturning Paton's original hypothesis that cannabis did not act on receptors. Dr Allyn Howlett, a pharmacologist at St Louis Medical School, who had done post-doctoral research at the University of Virginia involving the characterization of the first G-protein, along with Bill Devane a graduate student at St Louis, provided conclusive evidence, published in 1988, that cannabinoid receptors existed in the brain.²⁹ Howlett's work was confirmed by the cloning of the CB1 receptor in the 1990s.³⁰ Evidence of a cannabis receptor was then confirmed through other developments at the time in the field of cloning. Pertwee described the inter-relations,

*It was lucky the field was developing in parallel with these important advances Cloning was really in... so once it was cloned that was it, the receptor must exist.*³¹

Receptor cloning became a major preoccupation of molecular pharmacologists and by 2000 pharmacology had entered a new era.³² The distribution of CB1 receptors, found predominantly on central and peripheral nerve terminals, accounted for characteristics, described earlier by pharmacologists and the benefits described by patients in the 1970s and 1980s. A further receptor, a periphery receptor, CB2, was unexpectedly located by the pharmaceutical firm Sterling Winthrop in the UK in 1993, when it searched for an anti-inflammatory drug.³³ This discovery of a receptor outside the brain was important because it opened up the possibility of achieving a cannabis-like effect without the problems of cannabis, just as the pharmaceutical industry had tried to do with drugs like nabilone.³⁴

These discoveries led to the next crucial question: What was the role of this receptor system? Did the human body produce cannabinoid receptor agonists, chemicals that bind to the receptor, or did only the plant compounds affect the receptor?³⁵ Mechoulam's group provided the next piece of the jigsaw. Mechoulam theorized that there must be a chemical that originated in the body (endogenous) and sought to identify it. He commented later on the search,

*We assumed that these receptors are not found in our body because there is a plant out there but the brain forms some kind of compound that will activate these receptors when needed. So we started looking for these endogenous compounds.*³⁶

This was a complex process involving international and interdisciplinary co-operation, technological advances, and serendipity. Bill Devane moved to Israel to take up a post-doctoral position with Mechoulam and searched for the assumed endogenous cannabinoid. Devane, along with a Czech researcher Luis Hanus, synthesized a new radioactive probe, which they used to help identify the substance. A promising candidate was extracted from pig brain. Once they had material which seemed pure they utilized the advanced techniques of nuclear magnetic resonance (NMR) spectroscopy which provided the final formation of an endogenous cannabinoid, which was later termed Anandamide. Recent technological advances had made these discoveries possible as Mechoulam later elaborated,

*When we isolated Anandamide.....we had essentially nothing, we barely saw the material we isolated but the machines were happy with it.couldn't have been done twenty years earlier.*³⁷

Technological developments in the field made it possible to work with much smaller amounts of material and to considerably speed up research. Rang, in a history of receptors, explained the importance of such technological developments.

*It took a full year to make the binding measurements, carry out the necessary controls and estimate the binding parameters – a task now routinely performed by a technician in less than a day.*³⁸

Once the potential substance was discovered it was necessary to establish if it could activate the CB1 receptor, but Mechoulam's group lacked sufficient material to carry out the tests. Others within the cannabis network provided the solution. Pertwee's decision to stay in the cannabis field and develop bioassays proved advantageous. He later commented.

...I felt it was the way forward because you learn much more about the mode of actions... if you want go in vivo..it is very good for clinical

*relevance but if you want to find out how something works you are better off in vitro because it's a much simpler system. We developed a little assay based on vas deferens from the mouse which as it happens turned out to be stuffed full of cannabinoid receptors..... turned out to be very sensitive to cannabinoids.*³⁹

By the early 1990s, Pertwee had shown he was able to work on mouse vas deferens with tiny amounts of material. He presented some of the initial vas deferens data at a cannabinoid meeting in Palm Beach in 1991 and this led to collaboration with Mechoulam. Here luck played a role. Mechoulam and Devane sent Pertwee some impure material. Pertwee was able to discover that it paralleled THC in activity. On sending the pure substance it was found inactive. This confusion was later cleared up when it was discovered that the pure material had oxidised and thus disrupted the experiment, whereas the impure material contained an anti-oxidant and was still effective for Pertwee.⁴⁰ As a result, using the mouse vas deferens, Pertwee (with Graeme Griffin) was able to provide the first evidence that this substance, not only bound to cannabinoid receptors, but also activated these receptors, which strengthened the argument that Anandamide was an endogenous cannabinoid which acted upon the newly discovered receptors.⁴¹ Pertwee explained how it was serendipitous that they used the vas deferens assays as they had been working on other assays which could have provided a false trail.

*It was lucky we used this tissue, as gut chews up enzymes, so luckily, we used vas deferens. So we were able to detect something.*⁴²

The realization of the enormity of the impact of the discovery of the ECRS system had a range of broader implications. The excitement led to a re-emergence of funding for the cannabis research field. Pertwee described how a flow of research funding emerged.⁴³ The new tranche of funding brought in new researchers to the field. Pertwee received Wellcome Trust funding in the 1990s on a re-entry scheme, providing him with two new staff. An MRC co-operative scheme provided additional funding. The discoveries led to the reinvigoration of the cannabis network and the establishment of international cannabinoid societies to advance the course of cannabis research. It led to the integration with a number of other scientific disciplines other than pharmacologists

and psychologists, for instance, immunologists such as Dr. Klein, professor of medical microbiology and immunology at the University of South Florida, who was working in a new field of psychoneuroimmunology, all finding areas of interest in research on cannabis. After the discovery of the ECRS new dedicated international societies and symposia that were much more open to new researchers were initiated. The International Cannabinoid Research Society was set up in the year the receptor was cloned. The Society met annually to exchange findings and to facilitate collaborations between scientists as well as with the pharmaceutical industry. A specific society for research into medical applications, the International Association for Cannabis Medicine was set up by a German clinician.⁴⁴ These scientific networks consolidated the field in a way that had not previously been achieved.

The discovery of the ECRS re-stimulated cannabis research and opened up new avenues. Dr Vincenzo di Marzo, a researcher on endocannabinoids in Italy, explained its importance for cannabis-based medicines.

Some people view this issue as possibility separate from the re-medicalization of cannabis but in fact we were getting many hints from knowing how the endocannabinoids are made and how they are regulated and how to use the plant cannabinoids.⁴⁵

These developments provided cannabis therapeutics with a more acceptable face as they explained the mechanism behind anecdotal reports of cannabis' benefits, and the action of new cannabis-based drugs like nabilone. One reason the discoveries had such an impact on therapeutics was because the system impacted on so many aspects of the body. Mechoulam described the excitement around the discovery.

There is almost no major physical activity in which this system is not involved.... It provided the basis for a huge amount of work.⁴⁶

In later decades it would open up research especially on the modulation of pain, neurodegenerative disease, and anti-inflammatory action. Other research areas that were stimulated included immunity, leading to research on how the ECRS might help prevent re-occurring tumour growth; treatment for Post Traumatic Stress Disorder,

where it appeared it might play a role in emotions and memory function; as an anti-inflammatory agent; in the treatment of schizophrenia, and for some cardiovascular diseases. Alternatively, when the endogenous cannabinoid system malfunctioned, it appeared that it could lead to obesity, fertility problems, and stroke. The possibility emerged of manipulating the system to alleviate these disorders: a possibility that was of great interest to industry.

It was also important because it appeared to offer a way of avoiding one of the major hindrances to the use of cannabis as a medicine and one that had previously frightened off industry –the psychoactive properties of the drug. Iverson explained the significance.

Using THC, or synthetic or cannabis extract was always limiting....a narrow window between desired result and intoxication. THC would also go everywhere in the brain whereas the endocannabinoid system could be much more specific. The discovery of the endocannabinoid system provided the potential for eliminating the intoxication element.⁴⁷

That the CB2 receptor was located outside of the brain was of great interest to the pharmaceutical companies because of the possibility of achieving pain relief without the ‘high’. Other work by Pertwee’s group in Aberdeen led to the discovery of the allosteric site on the receptor.⁴⁸ This Pertwee described as acting rather like a volume control, allowing the activity of the receptor to be turned up or down.⁴⁹ A new aim of research became an attempt to develop new drugs to enhance the activity of the receptor. The discovery of the ECRS meant that pharmaceutical companies finally discovered a sustained interest because they could look for either agonist or antagonists (receptor blocking) drugs which would affect the ECRS. Iverson explained later the importance to medicine.

After all most of the drugs on the market...the new drugs over the last twenty years ... are based on being agonist or antagonist of receptors of endogenous compounds like dopamine and so on.⁵⁰

The goal was to take this new understanding in the laboratory and to make it feasible for use in the clinic but the time lag between discovery and when patients received the

benefits could be considerable. Iverson later commented,

*Thirty years from lab discovery to useful medicine takes many decades. So research is at an interesting stage. Modern neuroscience development will take a long time to reach maturity.*⁵¹

The discovery of the mode of action of cannabis, finally, caught the serious interest of pharmaceutical companies on two grounds. They could either produce a medicine directly based on cannabis, or they could move away from cannabis –based drugs to endogenous cannabinoids which would block (antagonists), mimic or augment (agonists) the endocannabinoid receptor system. Avensis, for instance, a leading pharmaceutical company, was attracted because of potential applications for treating obesity, potentially a high money earning applicaiton. The company developed synthetic antagonists and agonists such as SR141716a known as rimonabant marketed as Acomplia. The targeting of obesity, Sanofi argued had become a major public health concern, and one with potential mass market appeal for industry. Rimonabant was not without problems as it became linked to depression and Sanofi had to withdraw it from the market. But the discovery of the endocannabinoid receptor system had brought a novel dimension to research as this understanding allowed some research to move away from directly cannabis-based medicines like the synthetic THC-based Marinol. It opened up a whole new arena and would lead to drugs that were well outside the remit of the Misuse of Drugs Act or the international drugs control conventions.⁵² Drugs developed from this new understanding were still a long way off from reaching the clinic and over the next decade many studies remained focused on the plant-based or synthetic cannabinoids.

It was possible that the stigma around cannabis had created a glass ceiling for research, and permeated even these new approaches. Di Marzio commented how the stigma was difficult to dispel.

There has always been this kind of preconceived idea that those working in cannabinoids were doing something wrong...You can get an idea... how still the stigma is acting. There has been now – it's almost 15 years, it's 18 years, 19 years – since the discovery of the CB2 receptor, and there have been several CB2 synthetic, CB2 selective agonists for this receptor which

*are totally devoid of any psychoactivity so they could easily bypass all the problems of the psychotropic activity of cannabis and still we know very little about this.*⁵³

Nevertheless, there was an alteration in attitudes towards cannabis-based drugs by 1990. Cannabis derivatives like dronabinol were viewed more leniently in some quarters. The CND requested the WHO to review the dronabinol issue. WHO presented a recommendation to downgrade dronabinol as it acknowledged dronabinol's medical properties were greater than the substance it had to be classified alongside.

*It is nevertheless obvious in the assessment of the Committee that dronabinol has therapeutic usefulness that is definitely greater than that of the other substances in Schedule I which have very limited if any therapeutic usefulness and that it is comparable to that of a number of drugs in Schedule II.*⁵⁴

Furthermore, the WHO did not rate highly dronabinol's ability to adversely affect cannabis misuse as cannabis use was already widespread.

Since cannabis is controlled under the Single Convention.. changes in the scheduling of dronabinolwould not entail any change to the control status of cannabis. Nevertheless there might be a concern about the possibility that the official recognition of therapeutic usefulness of dronabinol might encourage the medicinal use of cannabis and thus its abuse. However cannabis is already the most widely abused illicit drug in the world...it is unlikely that such recognition would make a significant difference.

The CND was persuaded and at the 32nd meeting, recommended rescheduling dronabinol from Schedule I to Schedule II.⁵⁵ This still left it a tightly controlled drug and pressure built later for it to be further downgraded. In the UK however it was moved to Schedule 2 of the Misuse of Drugs Act Regulations placing it alongside morphine, though it remained an unlicensed drug in the UK and had to be imported for prescription on a named-patient basis. This left the legal responsibility with the doctor. Arguments increased for it to be further downgraded to Schedule IV of UN Convention, the lowest schedule and in 2002 the WHO recommended its downgrading to Schedule IV.

*The abuse liability for dronabinol is expected to remain very low so long as cannabis continues to be readily available...the committee considered that dronabinol should be reschedule to schedule IV of the 1971 Convention on Psychotropic Substances, and to avoid placing stereochemical variants of the same substance under different control systems the committee recommended that all stereochemical variants of delt-9-THC be moved to Schedule IV of the 1971 Convention.*⁵⁶

The 'stigma' of cannabis still operated and the recommendation was withdrawn on the recommendations of UNODC. In 2006 the WHO recommended instead that it be transferred to Schedule III as a compromise but faced strong opposition.⁵⁷ But the endocannabinoids especially Anandamide became major areas of study though none by this stage reached the clinic due to a lack of toxicity data. In the clinic the focus remained on THC, CBD and CBN.

The emergence of GW Pharmaceuticals, 1998-2007. Cannabis-based medicine extracts (CBMEs)

Another avenue for research was the re-investigation of herbal cannabis and this route took off in the UK with the development of a small biotechnology company based on the development of extracts of the cannabis plant. 1998 marked a new era in the development of cannabis-based medicines with the establishment of GW Pharmaceuticals in the UK, by the scientist entrepreneur, Dr Geoffrey Guy. GW achieved the first Home Office licence to cultivate, possess and supply cannabis for research. Cultivation began in August 1998 from which GW produced Sativex, an oral metered spray of a standardized extract from cloned cannabis plants. This marked a departure from the synthetic THC based medicines of the 1970s and 1980s. Sativex was based on the use of extracts and contained a mixture of THC and CBD in a 50/50 mixture.⁵⁸ Although at the time of writing Sativex is not yet approved in the UK, the creation and development of GW marked a watershed in the process of the medical use of cannabis, reflecting changes in the state of the pharmaceutical industry, relationships between industry, government, academia and patients, as well as developments in drug technology and clinical trial methodology. But why did 1998 see the entry and sustained development of a pharmaceutical company in the UK specifically based on cannabis?

Phytomedicine, the biotechnology industry and the role of the individual entrepreneur

The decision by the UK Government to grant GW Pharmaceuticals the licence necessary to initiate cultivation and devise extraction procedures equal to the task of producing standardised plant extracts of proven content and stability was both timely and judicious coinciding as it did with a renewed interest generally in plant-based medicines. It is also relevant that many researchers and patients have concluded that the whole plant is more effective as medicine than THC alone especially in the form of synthetic analogues.⁵⁹ - Geoffrey Guy.

Cannabis medicines in the nineteenth century had been based on herbal cannabis, usually in the form of a tincture, but these, in an era focused on active principles of plants, had fallen by the wayside. With the discovery of cannabis' active principle, THC, interest in cannabis had produced pills such as nabilone (Cesamet) based on one synthetic active principle of cannabis. GW was based on a different concept in which it aimed to capture something more akin to the whole plant. This alternative approach took place within the context of changes in pharmacy and developments in phytomedicine. For most of history, plants have been the main providers of medical drugs and even when pushed to the sideline there was a fluctuating but continuous interest in plant-based medicine.⁶⁰ Plant medicine was important early on: quinine and pyrethrum were the lynchpins for malaria treatment and control. At the very time when synthetics were at their height, and medicinal plants marginalized in the West some uncertainty existed over the former's long-term sustainability and hence there remained a residual level of interest in plant-based medicine.⁶¹ By the 1970s, the continuing threat of old diseases such as malaria, increased focus on diseases like cancer, and newly emerging diseases such as AIDS, combined with increasing drug resistance provided impetus to find alternatives and this included re-investigation of plants and a greater interest in synergistic effects. Equally, in the wider community concerns over biomedicine, and a vague unease that life had become too divorced from nature, increased support for 'alternative' medicine. In addition countries such as Brazil and China had retained an ongoing and important relationship with traditional plant medicine. Whilst reservations remained over the potential value and usefulness

of plants, increased acceptance of plant medicine emerged within the public, scientific circles and regulatory authorities. Mead discussed the role of botanical medicine in relation to developing international controls on cannabis.

*The natural foods movement reinforced by patient advocacy and empowerment has also given new vigour to the interest in botanical medicine and dietary supplements. Renewed support for botanical and other natural products has been accompanied by an increased distrust of the pharmaceutical industry and its new chemical entities...regulatory authorities have become more receptive to the concept of botanical medicines.*⁶²

Even though cannabis had lost its medical utility according to the WHO in the 1950s and cannabis tincture had been removed by 1973 in the UK, in some spheres there was a renaissance in the appreciation of plant-based medicine. This was reflected in the attitude of the National Cancer Institute in the US. Its screening programme for products, potentially helpful in the fight against cancer, initially excluded plants, but by the 1960s it was deemed advisable to incorporate them. Even with the advent of synthetic medicines, vast volumes of plants were used for drugs and new applications were emerging. For instance, two major developments, one in oncology with Taxol for cancer chemotherapy, and another around *Artemisia annua* for the treatment and prevention of malaria, encouraged the revival of interest in plant-based medicines and insecticides.⁶³ Primary health care accorded traditional medicine, in which plant lore was critical, a higher place within health policy. The Alma-Ata Conference of 1978 and the WHO *Health for All* report (1981) brought about a re-assessment of approaches to public health and one aspect of these changes was the increased consideration given to traditional medicine. A WHO report stated,

*The primary health care approach... also emphasizes the need to make maximum use of all available resources. This is why the International Conference on Primary Health Care, in Alma-Ata in 1978, recommended that governments give high priority to the utilization of traditional medicine and the incorporation of proven traditional remedies into national drug policies and regulations.*⁶⁴

The refocus on traditional medicine meant that plant-based medicines saw something of a revival from the 1980s onwards. In 1988 the World Conservation Union (IUCN) and the WHO collaborated to produce guidelines on medicinal plant conservation,⁶⁵ and significantly the WHO published *Traditional Medicine and Medicinal Plants*,

*The recent decision to make the traditional medicine programme part of the global programme concerned with drug management and policies recognizes the importance of plants as sources of products of medicinal value, and the need for an adequate technological infrastructure to realize the potential.*⁶⁶

Plants, however, provided a set of particular problems for industry.

Some of the problems of cannabis were related not only to its position as an illegal drug but to issues surrounding plant-based medicines in general. The problems highlighted in recent histories of plant-based medicines, like Taxol and *Artemisia annua*, can also be seen in the history of cannabis. These include issues over supply, isolation of active principles, standardization, and patents and these were a combination of negative factors that made pharmaceutical companies reluctant to invest. Goodman and Walsh's work on the history of Taxol illustrates this.

*Few companies are capable of extracting and purifying large quantities of Taxol. Scaling up required capital investment and given the general lack of interest both in natural product medicine and anti-cancer agents among pharmaceutical manufacturers, there was probably a reluctance to invest.*⁶⁷

With regard to cannabis therapeutics and the reason for the creation of GW to fill this niche, Guy elaborated some of these issues,

It was anticipated that one of the larger pharmaceutical companies would pick up the baton and use its vast drug development machinery to bring the project to fruition. Two major problems emerged. First, established 'big pharma' is not comfortable generally with development of phytomedicines from starting materials that have a history of abuse... It prefers an established drug development paradigm in which research is carried out to define the 'active constituent' This is thought to maximise intellectual property rights.second in an environment where opinion is divided

on the ethics of developing a cannabis-based product the boards of major companies probably reflect this dichotomy.⁶⁸

Established pharmaceutical companies, uneasy about working with cannabis left a space in the medical market place. The emergence of the biotechnology industry provided a new means to fill the space. The biotechnology industry, the industrial application of biological processes, took off after the discoveries around DNA in the 1970s in the US and developed in the UK after the 1980s.⁶⁹ As research and development and the cost of bringing drugs to market spiralled, acquisitions and mergers were commonplace in the pharmaceutical industry in the 1990s. National governments especially in Britain and Germany had recognized the potential of biotechnology and had encouraged their development via government initiatives and finance. New small companies emerged focusing on niche markets. This had a number of effects including some on the structure of industry. Quirke explained the impact of the changed environment.

It has brought back the inventor, in the person of the scientist-entrepreneur heading start-up companies. It has pushed big pharma into strategic alliances with start-up companies and academics and has led to the growth of what has been termed the bioscience industry.⁷⁰

The new structures encouraged innovation and biotechnology firms contributed new therapies.⁷¹ It was in this context that an entrepreneur in the biotechnology industry could start up a company to fill the niche with a plant derived cannabis-based medicine.

Geoffrey Guy, the founder of GW Pharmaceuticals, a physician with a degree in pharmacology from University of London had been involved in the pharmaceutical development of chemical entities, biotechnology products, and drug delivery systems. He summed up why he was the man to do the job.

There was no-one else who was interested in making, or thought it was remotely possible to make, a medicine out of cannabis...I'd had twenty years in narcotic analgesics, drug delivery, plant medicines and had just retired two days earlier...and had the time to think.⁷²

He had had a long term interest in plant-based medicines and had founded Phytopharm PLC in 1990 which developed novel products from medicinal plants, and which he floated in 1996. Guy explained the regulatory difficulties that had emerged when working on plant-based medicines in an era that concentrated on single chemical entities.

Since the war, and certainly since the 1960s and the Dunlop Report and afterwards, the medicines regulation pertained to single chemical entities. The prospect of developing a medicine, which contains something like 420 chemicals in the modern regulatory environment, was considered in the late 1980s–mid-1990s, to be pretty nigh impossible.⁷³

He became interested in building on his experience of plant-based medicine and aimed to ‘*bottle the essence of cannabis*.’ This meant the use of more than one active ingredient of cannabis and the use of herbal synergism. Scientists had been arguing since 1900 over the relative value of the alkaloids in cinchona and possible benefits of drug combinations. In the 1990s Kirby, a member of the Department of Medical Parasitology, at the London School of Hygiene and Tropical Medicine developed the argument that a herbal mixture was more effective than the use of a single active principle. Combination drug therapy, for instance, had been developed in the AIDS field.⁷⁴ The decision of GW to use a mixture of extracts from cannabis in order capture its essence, was in stark contrast to earlier industry moves. In following this route, GW set out to produce something closer to the plant-based product smoked by many patients.

The establishment of GW reflected the relationship between industry and science. Historians such as Oudshoorn have shown how the demarcation between industry and universities has become increasingly blurred since the early twentieth century.⁷⁵ Lowy has demonstrated how the pharmaceutical industry in particular has historically developed through unusually close association with academic researchers.⁷⁶ In the case of cannabis this knowledge exchange between industry and academia proved crucial and active attempts since the 1990s were made to integrate the two worlds. By the 1990s, international networking and the development of symposia facilitated an exchange of ideas, and importantly opened a window to industry. The formation of societies on

cannabis such as the International Cannabinoid Research Society brought companies into contact with academics.⁷⁷ Guy expanded on how one of these conferences re-stimulated his interest in the subject.

I went to a conference in London..and ... I thought: 'Ho hum, this is interesting. I thought it was...very taboo.'and there was the MCA (Medicines Control Agency), the Home Office, some very eminent scientists...patients and patient groups, and a little smattering of pharmaceutical people... keeping their heads way, way down, because they didn't want to be seen at a cannabis conference. The question arose: if research is to be done on cannabis, how do you standardize it?I stood up, spoke from the floor...and said that it could be done as long as you got the agreement from the Home Office, from the MCA.⁷⁸

These meetings which were stimulated by the involvement of professional bodies are discussed in detail in chapter seven. As with many new biotechnology firms GW capitalised on networks between industry and academia. The company created an internal Cannabinoid Research Institute (CRI) directed by Philip Robson, a consultant psychiatrist from Oxford who in 1996 had provided a review on the therapeutic use of cannabis for the Department of Health. The CRI was designed to provide links between commercial enterprise and academia.⁷⁹ GW Pharmaceuticals began collaborations with many of the major players in the field of cannabis research including Professor Roger Pertwee, who was engaged as Director of Pharmacology. Pertwee remained based at Aberdeen University but received funding from GW Pharmaceuticals to carry out work on plant cannabinoids. Further links were developed with Mechoulam, and di Marzo. These networks between science and industry allowed both to benefit from each others expertise.

To start-up such a firm involved a high level of risk and nowhere more so than in the case of cannabis where fears over safeguarding intellectual property rights and overcoming difficulties related to international drug controls made most other people steer well clear of the subject. Robson described some of the risks involved.

At that time in every country it was completely illegal. So in order for the thing to get off the ground you've got to convince the Home Office to give you a special licence which no one had done. Guy risked money before the

*Home Office came round to his repeated requests. There was no guarantee this would happen...he took the risk and put his own money up.*⁸⁰

The legal situation surrounding cannabis was still a major issue. But pressure from medicinal user activists provided incentives for policymakers to define the boundary between therapeutic cannabis and recreational cannabis, a division which the synthetic drugs like nabilone had failed to achieve. As is discussed in detail in chapter six, patient pressure that developed in the 1990s had kept the issue of therapeutic cannabis high on the agenda. Guy commented that *'the government was very concerned about the MS patients being pushed up Whitehall as a campaign to have cannabis legalized.'*⁸¹ By 1997 industry and policy interests were beginning to move in a similar direction.

Cannabis was a highly unusual substance in that it muddled the boundary between a medical and a recreational drug and one that already existed in herbal form for both uses, in the public domain. This scenario provided ammunition to both those in favour of medicalizing cannabis and those determined to prohibit it. Robson expounded the difference between bringing any new drug to market, in contrast to bringing cannabis to market and the potential benefits of doing so from a legal and public health viewpoint.

*The stuff is already out there in a totally unregulated way, manufactured by criminals whose quality control interests are not really at the forefront of their priorities. It's a paradox because if cannabis-based medicine was pharmaceutically produced and regulated a proportion of people currently running a risk by smoking illegal cannabis of uncertain strength and purity would switch to the pharmaceutical product and therefore even if there was a an inherent risk in cannabis-based medicine you would be teasing out all the additional risk of smoking an unstandardised, possibly adulterated drug. Also its illegal nature...the simple fact they could be arrested, even if not harmed directly by the medicine. It's a total mystery to me why regulators wouldn't factor that into their calculations.*⁸²

Some of these considerations were being gradually taken on board. Guy had approached government previously about producing a cannabis-based medicine but had been advised to maintain his interest in opiate-based medicines research. He recalled,

In the early 1990s we'd approached the Home Office and said: 'I'd be interested in looking at cannabis,' because, as you know, we'd dealt with the opium plant with opiates. We got a bit of a flea in our ear actually: the Home Office in the early 1990s said, 'No, you're going to stick with your opiates.' And, like any other pharmaceutical company or chairman, I thought that we had other fish to fry, and so we did.⁸³

However, as is discussed in chapter seven, attitudes had shifted by 1997 and a major report by the House of Lords on therapeutic cannabis pressured for industry involvement.⁸⁴ As far as Robson was concerned the House of Lords report conferred credibility and was vital to give the confidence for industry involvement. *'I don't think there would have been a GW if there hadn't been a House of Lords.'*⁸⁵ The significance for industry was that it opened the way for clinical trials and potential licensing of a cannabis-based medicine.

The need to split medical arguments from calls for legalization provided a spur to re-medicalization. Confidence was boosted when David Blunkett, the Minister of Health, appeared supportive when he stated, *'should as I believe... this programme be proved to be successful I will recommend to the Medicines Control Agency that they should go ahead with authorising its medical use.'*⁸⁶ Edwards described the pressure for additional pain medicines.

So, I think the official mind-set would have been...was that one should be very willing to determine the therapeutic value of THC, even if it were dangerous because we knew we needed better drugs for pain relief. The pain specialists really made us feel a bit ashamed if we thought that morphine and heroin were enough they weren't. We needed better drugs.⁸⁷

Guy described how the government position did not deviate from its overall aim: to facilitate research and see the development of a pharmaceutical grade product in order to eliminate the argument for legalization on medical grounds.

If a product could be approved by the MCA as an approved medicine then the government would move to reschedule that product – not cannabis – not the plant, not the raw material, but that finished product – they would reschedule it to an appropriate schedule so that it could be used as a medicine. Therefore it was the government's position before I even got

involved with them because their concern was, if there is a medicine here, you have to separate it from the advocacy debate. That's what was done, very, very straightforward and very quickly then... The government was entirely consistent all the way through, and we got an enormous amount of support from the Home Office, even directly from Cabinet Office in the early days to ensure that this programme would run ahead smoothly.⁸⁸

If government had determined this was the way forward they needed to attract industry interest. Guy described how the doors were opened for his company at a witness seminar held in 2009

Paul Boateng opened the meeting and said, 'Her Majesty's Government has no will to reschedule cannabis', at which point everybody's eyes went to the ceiling. 'However,' he said, 'we'd like the research to be done.' At which point most people thought: 'Well, this is bizarre.' But he did suggest that if one wanted to do the research, one should approach the Home Office Drugs Inspectorate (HODI). Having worked in one of the most highly regulated environments the previous 20 years with opiates and with a range of materials like that, when a minister says: 'Go and see my officials' that's what we did.'⁸⁹

Guy met with the Home Office Drugs Inspectorate and was surprised at their rapid response.

We presented to the Home Office in the January 1998, and I nearly forgot about it again, because I thought it would be buried in there for two or three years. About four weeks later I received a phone call from the Chief Inspector of the Home Office, whom individually is probably more responsible than anybody else in this room for the progress of our programme, and that's Mr Alan Macfarlane. He rang me up and said: 'We'll do this. We don't know how we're going to do this: could you put a proposal in?'⁹⁰

GW was granted a Home Office licence to grow cannabis in June 1998 and was granted a clinical trial exemption certificate to conduct clinical studies with cannabis-based medicine extracts for numerous applications. With these permissions in place, GW was sufficiently confident to start the first large-scale, legal commercial production of cannabis for medicine in the UK.

Learning to grow cannabis: Standardization, security and patents

*Uniformity is king. Everything we do strives to produce batch after batch of plant material which is almost the same as the one before.*⁹¹ – David Potter, GW Pharmaceuticals.

GW solved the problem of supply that had plagued cannabis research by turning to vertical integration, producing both the raw material and finished product. The main issue for GW was the need for standardization of the raw material. In describing his work, the chief botanist at GW Pharmaceuticals, Dr David Potter, highlighted the importance of standardization.⁹² Standardization was another reason why industry steered clear of plants. They were products where external and uncontrolled forces, climate, for instance, could make it difficult to achieve standardization of relative levels of active ingredients and therefore dose. Goodman described the problem for Taxol, *'Yield and weather conditions were two elements that could not be controlled and had a considerable impact on the planning of clinical trials.'*⁹³ For GW one of the main aims became the production of pharmaceutical grade cannabis, through the growing of genetically identical material in optimum uniform conditions.

Security issues had to be resolved. The placement of cannabis within the drug control mechanisms meant that special requirements for the site had to be met. A site was found where a security system was already in place and which also provided a well-equipped research glasshouse and half an acre of space. Apart from his botanical knowledge, Potter also brought with him useful police contacts built up in his earlier career in pesticides, and this facilitated the development of good working relationships with the police and Home Office. Providing the necessary security was feasible but expensive, and later the site was split to spread risk. The Home Office was particularly nervous of any diversion of plant material so traceability of plant material was critical. Any failure to trace a particular plant and tally numbers on any particular day during a regular visit by the Home Office resulted in nerve racking moments. Potter described the paperwork as phenomenal.⁹⁴ Each plant had a unique number and any movement, harvesting, or destruction had to be logged. Failure to meet Home Office requirements could have resulted in the removal of the licence and failure of the project. Over time

the relationship with the Home Office and police settled down and a spin off was that the company could provide the police and the Home Office with specialist training courses on cannabis.

A standardised product was a priority and for this botanical knowledge was an essential forerunner. The first employee Dr David Potter had seventeen years experience working for Shell on pesticides, and he was experienced in the process of registration of novel compounds. Suitable plant material had to be sourced and as this was the first time cannabis was grown commercially on this scale in the UK, intellectual knowledge about growing the plants had to be acquired. This is where a company called HortaPharm BV in the Netherlands proved useful. Staffed by expatriate Americans, banned from working in the United States, they had foreseen a time when there would be a demand for a range of cannabinoids, not just those producing high levels of THC. HortaPharm had combed the world for different seeds and created a seed bank from which they had cross-bred plants to produce varieties with high degrees of cannabinoids such as CBD. GW bought the rights to HortaPharm's collection and capitalised upon the firm's intellectual knowledge. International regulations forbade the movement of plants from Holland to the UK, and as there was no system for Home Office permits for plants, only seeds, which did not fall under international regulation, could be transported. HortaPharm was able to return to their parent plants to produce seeds that would produce similar progeny. These yielded eight packets of seeds of the most promising lines containing pure lines of CBD and THC. Eventually, as GW established itself, it was able to obtain licences for HortaPharm's collection of plants, which was removed to the UK, providing a resource which could be dipped into when necessary. On the 24th August 1998 the eight varieties produced by HortaPharm were planted and ten days later yielded the first two thousand seedlings. HortaPharm provided the know-how to take the cuttings and GW developed the process. Plants with the highest cannabinoid concentration and purity were identified and ten genotypes selected and five recommended for trial. These five chemovars (chemical varieties) were selected for commercial cultivation. Thus GW had successfully bred the raw material and was therefore in a position to mass produce standardized or rather genetically identical plant material cloned from the original mother-plants raised by HortaPharm in 1984.

GW had to be able to be able to control the growing environment. Potter expanded on the need for standardization in phytomedicine.

*Medicinal cannabis must be of consistent quality. In striving to produce cannabinoids of uniform high quality commercially, the pharmaceutical company needs to ensure that plant material with the most appropriate genetics is selected for the propagation process...the correct environment has to be found in which this material can be propagated, carefully harvested and stabilised by prompt drying.*⁹⁵

Growing the plants to maturity, GW fine-tuned information from HortaPharm and incorporated knowledge gleaned from illegal growers. Varieties resistant to pests, plant density, the growing medium and humidity levels were all factors to be ascertained and controlled. Optimum conditions were found for these via a process of trial and error, and serendipitous discovery. One major issue was that the company needed to grow plants north of the equator whereas cannabis that produces a higher concentration of active ingredients does not grow naturally in light levels found in the UK, nor would it produce sufficient harvests per year needed for commercial mass production. Lighting in the glasshouse had to be supplemented to achieve standardized light levels and therefore yields. The timing of harvesting was critical: a week early or late affected yields. Plants were cultivated in accordance with Good Agricultural Practice (GAP) methods of the European Medicines Evaluation Agencies and in conjunction with the Medicines Control Agency, for the production of a Botanical Drug Substance.⁹⁶ Standardised cannabis plants were then processed to produce the medical product Sativex.

Intellectual property right protection was essential for the company. In the past companies tended to steer clear of plants due to difficulties of obtaining patents, and those that risked involvement, faced debates over issues of bio-piracy.⁹⁷ There were fears raised over the ‘hijacking of an ancient and folk remedy’ and the patenting of traditional knowledge.⁹⁸ But standardization was a means of achieving property rights over the end product. GW was able to exploit this because it could certify to a new variety as defined by the demonstration of distinctiveness, uniformity and stability, therefore gaining European Plant Breeders Rights. This process would normally be carried out in

the UK but because of security issues plants could not be assessed in the UK and had to be exported to Holland, incurring further difficulties over import and export licences, a process which caused some amusement at customs – carrying cannabis to Holland?!⁹⁹ Achieving standardization therefore provided the opportunity to obtain intellectual property rights, a necessity to make a high risk investment worthwhile, as it allowed GW to license chemically and genetically characterised extracts of *Cannabis sativa* L. - CBD and CBN protected as Tetranabinex® and Nabidiolex.

Was all the effort worthwhile? After three years GW was ready to test the product. Concerns over the impact meant that early tests on humans involved a ratio of one patient to thirteen doctors waiting to see what would happen. One patient became ‘high’ rapidly and described the medicine as powerful, like two joints of the best cannabis. Potter described the excitement, ‘*it told us we’d managed to capture the essence of cannabis in a bottle.*’¹⁰⁰ Whilst not the effect desired for a medicine it proved that GW had achieved an action more closely related to that of herbal cannabis.

GW Pharmaceuticals’ decision to develop a new delivery system rather than stay with the oral administration method used for dronabinol (Marinol) and nabilone (Cesamet) leads to the question as to how far technical change has helped to define boundary change? Producing oral cannabis medicines in the 1980s had been important as a delineator of medical/ non-medical boundaries, and continued to be important especially in a climate increasingly against smoking. The spread of no-smoking zones to include hospitals, and fears over lung damage precluded the smoking route for acceptable evidence-based medicine. However oral medicines had their detractors and developments of alternative delivery methods have been important in the story of cannabis-based medicines. It appeared patients generally disliked available oral cannabis-based tablets as they had a long lag time and poor absorption. Nor was an oral route satisfactory for those suffering from nausea: this was one reason why tablets of dronabinol and nabilone were not well used. Intravenous and inhalation remained the quickest routes of absorption. But both had problems. Inhalation was initially proposed but presented technical problems.¹⁰¹ Russo showed how GW modernized the nineteenth century technique of an extract in an ethanol base by utilising supercritical

CO2 extraction. GW, therefore, piloted propellant powered aerosols providing a fluid extract of a metered spray under the tongue or inside the cheek. This method allowed for reliable and rapid absorption and one with which patients could self-titrate. Self-titration was important. Notcutt recalled, *‘I think that during the 1990s we also got used to the concept of patient-controlled analgesia after surgery.’*¹⁰² It put patients back in control of dosage. Development of delivery methods has been historically important as delivery methods and technological developments could provide intellectual property rights. This was an essential aspect of working with botanical products. GW developed specialist security technology that could be incorporated in all its drug delivery systems allowing recording and remote monitoring of patient usage to prevent any potential abuse of its cannabis-based medicines. This technology enabled industry to further remove medical cannabis away from fears over misuse. By 2001 the company was ready to start clinical trials with Sativex.

Conclusion

Re-medicalization was intimately linked with developments in the pharmaceutical industry. Over the period under study the pharmaceutical industry developed a greater interest in cannabis as a potential medicine. Initially, academic research had struggled without an industrial supply but from the 1970s interactions between academia and industry boosted re-medicalization and the development of cannabis-based medicines. Nabilone and dronabinol set a precedent for the use of cannabis-based medicine and provided the cannabis therapeutics field with a new legitimacy. However, the relative failure of these synthetic, single chemical entity drugs left open the door to patient pressure for access to cannabis and later forced a re-evaluation of herbal cannabis. Pharmaceutical interest was re-stimulated when industry compounds contributed to new understandings of the mode of action of cannabis. This opened up two routes for industry involvement. First, drugs designed to manipulate the cannabinoid receptor system which moved drugs away from the use of cannabis itself. Second, industry involvement, stimulated by developments in phytopharmacy, moved research back in the direction of plant-based medical products, and linked it more closely to the

traditionally smoked herbal cannabis or the original herbal tincture of cannabis, whose mechanism of action had been revealed.

In the UK, GW Pharmaceuticals and its development of Sativex spurred the re-medicalization of cannabis by the provision of a product more concurrent with developments in standardization, clinical trials and drug regulation. Development of a new drug delivery system, which was more effective and faster than the tablets used for the delivery of synthetic THC, and which steered clear of smoking, fitted within acceptable treatments but also took on board patient concerns. If a licence was to be achieved for Sativex in the UK it would be a remarkable development in the process of industrializing cannabis. First, it would bring a cannabis-based drug back into the medical marketplace after withdrawal of the extract. Second, although cannabis-based drugs like Marinol (dronabinol) have been on the market since the mid 1980s, these were based on synthetic THC while Sativex consisted of extracts of cannabis not synthetic derivatives. Third, Sativex was based not on the use of one single active principle but on a combination of extracts of both THC and CBD, in an attempt to get closer the 'whole plant.' Fourth, a new delivery system had potential to provide the benefit of smoked cannabis without its negative connotations. By 2001, GW was ready to start large-scale clinical trials and was developing a portfolio of drugs and was working on a range of applications beyond its start point of MS. To bring its CBME product to market, Sativex had to pass successfully through the benchmark double-blind randomized clinical trial and through the UK regulatory and licensing mechanisms. The following chapters consider the factors that contributed to the development of GW pharmaceuticals and the process of Sativex products through clinical trials and regulatory mechanisms.

¹ J. Slinn, 'Research and Development in the UK Pharmaceutical Industry in the 19th Century to the 1960s,' p.186; L. Hill-Curth, *From Physick to Pharmacology: Five Hundred Years of British Drug Retailing* (Hampshire: Ashgate, 2006).

² J. Slinn, 'The Development of the Pharmaceutical Industry,' pp. 155-174.

³ Ibid.; V. Quirke, 'From Alkaloids to Gene Therapy', pp.177-201.

⁴ Goodman, and Walsh, *The Story of Taxol*, p.144.

⁵ Interview with R. Mechoulam.

⁶ House of Lords Select Committee on Science and Technology, *Cannabis: The Scientific and Medical*

Evidence, 9th Report, (London: TSO,1998), K. Coe, reported by Iverson, L.. Notes on Conference “Marihuana and Medicine” at New York University Medical Center, New York, 20-21 March 1998,Appendix 3.

⁷ Slinn, ‘Research and Development’, p.170.

⁸ M. Mathre, ‘Cannabis Series- the Whole Story Part 4 The Medicinal Uses of Cannabis Pre-Prohibition,’ 2 (4) (2002), p.5; Iverson, *The Science of Marijuana*, p. 143.

⁹ BMA, Therapeutic Uses of Cannabis, p. 22.

¹⁰ FDA, available from: <http://www.fda.gov/NewsEvents/Testimony/ucm114741.htm>_last accessed 23 March 2010.

¹¹ An isomer is a compound with the same molecular formula but different structural formula. For instance the compound contains the same number of atoms of the same elements but these are arranged in a different structure thereby providing different properties.

¹² McAllister, *Drug Diplomacy*, p. 230

¹³ Iverson, *The Science of Marijuana*, p. 144.

¹⁴ Ibid.

¹⁵ Since 2000 these drugs have experienced something of a revival. Nabilone was bought by Valeant Pharmaceuticals from Eli Lilly and approved by the FDA in 2006 and in 2007 Valeant Pharmaceuticals acquired the rights from Cambridge Laboratories to market Nabilone in the UK.

¹⁶ WHO, *Expert Committee on Drugs Liable to Produce Addiction*. 26th Report, Technical Report 1989, No. 787, (Geneva: WHO, 1989).

¹⁷ Quirke, ‘From Alkaloids to Gene Therapy, p.197.

¹⁸ Slinn, ‘The Development of the Pharmaceutical Industry,’ p. 93.

¹⁹ Interview with Roger Pertwee.

²⁰ Ibid.

²¹ Endogenous refers to substances that originate within an organism, so in relation to cannabinoids in essence meaning substances that originated in the human body rather than the plant.

²² Any of a class of cell membrane proteins that function as intermediaries between hormone receptors and effector enzymes and enable the cell to regulate its metabolism in response to hormonal changes.

²³ G. Hill, ‘G-Protein-Coupled Receptors: Past, Present and Future,’ *British Journal of Pharmacology*, 147 (2006), pp. S27-S37.

²⁴ Interview with R. Pertwee. G-protein coupled receptors are cell surface receptors which bind to G-proteins and are involved in chemical signaling between nerve cells.

²⁵ Hill, ‘G-Protein-Coupled Receptors’, pp. S27-S37.

²⁶ Pertwee, ‘Cannabinoids Pharmacology, p.S169.

²⁷ Interview with R. Pertwee.

²⁸ In biochemistry, a receptor is a protein molecule, embedded in either the plasma membrane or the cytoplasm of a cell, to which one or more specific kinds of signaling molecules may attach. A molecule which binds (attaches) to a receptor is called a ligand, Each kind of receptor can bind only certain ligand shapes. Each cell typically has many receptors, of many different kinds.

²⁹ W. Devane, F. Dysarz, M. Johnson, L. Melvin and A. Howlett, A. ‘Determination and Characterization of a Cannabinoid Receptor in Rat Brain’, *Mol. Pharm.* 34. (1988). pp. 605–613.

³⁰ CB1 receptor.

³¹ Interview with R. Pertwee.

³² H.P. Rang, HP. ‘The Receptor Concept: Pharmacology’s Big Idea’ *British Journal of Pharmacology*. 147, (2006). pp. S9-S16.

- ³³ Interview with R. Pertwee.
- ³⁴ Ibid.
- ³⁵ An agonist is a term used to describe a type of ligand that binds and alters the activity of a receptor.
- ³⁶ Interview with R. Mechoulam.
- ³⁷ Ibid.
- ³⁸ Rang, 'The Receptor Concept,' pp. S9-S16.
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- ⁴¹ W.A. Devane, *et al*, 'Isolation and Structure of a Brain Constituent That Binds to the Cannabinoid Receptor' *Science*, 258 (1992), pp. 1946-1949.
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- ⁴⁵ V. di Marzio, speaking in a witness seminar and the re-medicalization of cannabis in S.M. Crowther, L. Reynolds and T. Tansey, *The Medicalization of Cannabis*.
- ⁴⁶ Interview with R. Mechoulam.
- ⁴⁷ Interview with L. Iverson by Suzanne Taylor 2007.
- ⁴⁸ A site on an enzyme molecule which binds with a non-substrate molecule, inducing a conformational change which results in an alteration of the affinity of the enzyme for its substrate.
- ⁴⁹ Interview with R Pertwee.
- ⁵⁰ Interview with L. Iverson.
- ⁵¹ Ibid.
- ⁵² Interview with R. Pertwee.
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Chapter Six

Forces of necessity: The role of lay knowledge, and advocacy, 1973-2004

Self-help and self-medication had always been important in health care and health activism, despite the increasing role of the National Health Service, became important in the health arena in the post-war period. This activism was part of a wider trend as activism in general took on a renewed format in the 1960s. The emergence of organisations and charities in particular in relation to poverty such as Shelter, and the environment such as the World Wildlife Fund, played an increasingly important role in society. Berridge has described the growth of single-issue health pressure groups like Action on Smoking and Health (ASH) established in the 1970s. These were single issue, media aware, national organizations.¹ Within this context cannabis and activism became increasingly intertwined from the 1960s. Medical activism was one aspect of cannabis campaigns. Grass roots knowledge of drugs proved important to the growing relationship between lay and professional spheres and as part of this trend lay knowledge around cannabis and subsequent patient activism was instrumental in the process of re-medicalizing cannabis. Medical activism in relation to cannabis evolved considerably during the period studied and this chapter charts its evolution and impact on the re-medicalisation of cannabis. Initially, activist focus was on legalization namely for recreational purposes, and medical use cited as one reason for this demand. In the US activism developed by individual patients by the 1980s and 1990s and later patient associations campaigned for medical access to cannabis. This time activists distanced themselves from calls for legalization on recreational grounds. Stimulus to calls for medical access first came from the growing acceptance of cannabis as a treatment for cancer chemotherapy. The AIDS crisis of the 1980s and the ensuing search for treatments brought added stimulus to debates over access to cannabis leading to the creation of new activist groups and co-operation with pre-existing cannabis activists. In the US it led to subsequent changes to policy with the setting up of compassionate programmes in some states and the licensing of nabilone (Cesamet) and dronabinol

(Marinol). In contrast, in the UK, whilst activism has been as relevant to the re-medicalization of cannabis as in the US, the impetus came from a different quarter. In the UK it was the pressure of MS sufferers that had the most influence and led to MS becoming the major stimulus for cannabis research. Patient advocacy of cannabis in the 1990s became critical to the process of re-medicalization, both through patient associations that campaigned on cannabis as part of a wider policy and activist groups that were set up as single issue campaigning associations to campaign for access to cannabis. The development of cannabis as a medicine especially since the 1980s has been brought about to a large extent by patient-led demand driving the scientific community, policy advisors, and industry to build upon anecdotal and scientific knowledge. Despite major advances in the knowledge base and development of clinical trials, from the patient perspective, development of licit cannabis-based drugs remained limited and access to cannabis-based drugs constrained. This chapter considers the role of lay knowledge around cannabis and the establishment of patient activist groups. The role of MS patient groups in influencing laboratory science, clinical research, the policy environment, and industry is examined. The complexities of the interface between these activist groups and the scientific and policy establishment in the advocacy of an alternative and illegal substance are highlighted.

Early lay knowledge and activism: Cannabis and drug liberalization

Cannabis activism in the 1960s focused on drug liberalization. In some cases it extolled the medical properties of the drug but medical arguments were subsumed within the larger campaign. In the UK, perhaps the most well known pressure group which campaigned for drug liberalization was SOMA, (Society of Mental Awareness) a campaign and research organisation founded by Stephen Abrams in 1967.² At the point where cannabis was coming under scrutiny in the Wootton Committee, the Society attempted to influence policy via the media and public opinion with the placement of an advertisement in the form of a petition in *The Times* on the 24th of July 1967³. The intention was to influence the terms of reference of the Wootton Committee into detailing the case for law reform.⁴ SOMA capitalised on its professional membership which included a medical network comprising a physician, pharmacologist, and a

research psychologist and the petition was signed by sixty five public figures, including Francis Crick, the co-discoverer of the structure of DNA, nine doctors, MPs including Brian Walden and Tom Driberg as well as the Beatles and Graham Greene. Such advocacy appeared to have little policy impact at that time, and the Wootton Report was rejected by government.

These politicized campaigns for legalization failed in an increasingly hostile policy environment. Medical cannabis was overwhelmed by a combination of the link to recreational use and limited proof of medical efficacy. Against this backdrop activism had mixed fortunes. Single issue groups could be relatively short-lived and SOMA hampered by a lack of funds, folded.⁵ Other voluntary drug organisation such as Release continued and others emerged throughout the 1970s. In the US the National Organization for the Reform of Marijuana Laws (NORML) founded in 1970 lobbied for the decriminalization of cannabis. In the UK in 1978 the Legalise Cannabis Campaign (LCC) was initiated to campaign for full legalization of the use and distribution of cannabis. As cannabis was no longer available as a medical product the campaign urged that cannabis should be available for prescription by doctors without special licensing requirements. Whilst ultimately groups like SOMA and the LCC had little success and placed emphasis on legalization they did use medical necessity as part of their argument and this raised awareness at the grassroots and in influential circles that there were possible medical uses of cannabis at a time when these uses were being denied and prohibited. But advocacy by patient associations for cannabis as a treatment for specific medical problems, disassociated from cannabis legalization, was to have a much bigger impact in the following decades.

Lay knowledge and medical activism, 1975-1991

Though side-lined, self-medication remained important despite the increased professionalization of medicine. With increased recreational cannabis use, lay knowledge developed around the therapeutic usages of the drug and activism related specifically to the medical use of cannabis emerged in the late 1970s and early 1980s. Health activism based around the concept of access to cannabis for medical necessity

became prominent in the US. The events in the US influenced later developments in the UK and UK campaigners developed links with US organizations. In the US Robert Randall, a glaucoma patient, defended his use of cannabis on the grounds of medical necessity and importantly won his case in court in 1975⁶. Randall was provided with access to government grown cannabis. After the Federal Drugs Administration (FDA) attempted to block access, Randall brought a case against the FDA in 1978 and won. This legal victory meant that the US government had to create the Investigative New Drugs Programme (INDP) in 1978 to supply National Institute of Drug Abuse grown cannabis to approximately thirty qualifying patients. This success encouraged patients to come together to campaign for legal access to cannabis for specific medical problems, creating a different agenda and separate from campaigns for legalization. Health activism became an increasingly important part of the story from the 1980s. Some potential medical uses for cannabis, for instance, in glaucoma had not attracted the same level interest as had the management of cancer treatment, yet were areas that lacked effective treatments. Consequently, user activism developed on a larger scale campaigning, not for access for a few individuals, but, rather, for reform of the laws that denied access in the first place. Robert Randall went on to found the patient association, the Alliance for Cannabis Therapeutics in 1981 along with Alice O'Leary. The association was set up with the express aim to campaign for the reform of laws which prohibited medical access to cannabis.⁷

Activism developed around diseases that lacked effective treatments and for which cannabis appeared to offer some hope but was yet to be investigated or deemed acceptable. The introduction of cannabis based-drugs in the 1980s contributed to a change in attitude towards cannabis therapeutics in policy circles in the US and the UK, from which activists benefited. In the UK, the findings of the 1980 Expert Group on Cannabis set up by the ACMD reflected a changed attitude towards cannabis. The dangers of cannabis were downplayed and attention began to focus on the possible benefits of the drug.⁸ It was work in one aspect of therapeutics that significantly contributed to this outcome and that was for the treatment of the side-effects of cancer chemotherapy. The urgent necessity to alleviate iatrogenic symptoms meant that cannabis gained its first modern instance of legitimacy. The need to use it in

this situation drew it away from discussion of recreational misuse. Significantly, it established a precedent from which other applications would later follow. However, the legitimacy was accorded to drugs based on synthetic THC rather than cannabis per se. Whilst the problems of cancer chemotherapy quickly stimulated research and acceptance yielding the licit drug nabilone licensed in 1982 in the UK, and shortly afterwards dronabinol as Marinol in 1985 in the US, there appears to have been limited activism in relation to cancer related drugs: there was no need as patients had licit access to cannabis-based drugs.

The HIV/AIDS crisis of the 1980s and 1990s provided the next spur to activism around cannabis. Russo, an historian of the American medical cannabis experience commented on the importance of the AIDS epidemic on attitudes towards cannabis.

The experience of desperate AIDS patients using medical marijuana helped to change the national perceptions of the drugs from menace to medicine.⁹

By 1993, the US Department of Health had listed AIDS as the most common cause of death for men aged 25-44.¹⁰ The advent of AIDS has been shown to have had a considerable impact on many areas of health policy. As a deadly new disease doctors lacked knowledge of the causation and treatment and looked for solutions beyond mainstream medicine.¹¹ Even after the viral agent was identified patients faced the reluctance of pharmaceutical companies to become involved and with a dearth of treatment options, patients were forced to look to self-help methods of treatment. Russo has argued,

The sudden emergence of the AIDS epidemic and the initial lack of effective treatment politicised the patient population into demanding quicker developments of, and access to, promising medication.¹²

Cannabis was one of the potential remedies and AIDS was 'a crucial influence on the growth of support for the medical marijuana movement.'¹³ By 1985, after pressure from the National Cancer Institute, more orthodox anti-viral treatment, including AZT, was developed for AIDS. However, a side-effect of AZT was nausea, leading to weight loss which exacerbated the problem of the wasting syndrome. Herbal cannabis became

popular in self-help circles as it acted as an appetite stimulate against the wasting syndrome, but its usefulness was compromised by its illicit status which forced patients into criminal activity.

Activism by AIDS patients for medicines such as cannabis was led by an active and well-organised gay rights movement. The experience and ready-made network of campaign groups like the ACT proved invaluable for AIDS campaigners. Randall had set up the ACT to campaign to protect medical users from the law and had mainly focused mainly upon cancer and glaucoma patients but, by 1983, ACT turned its attention to the AIDS issue. Though cannabis-based drugs had entered the market, these were not available for applications other than as a palliative in cancer treatment and herbal cannabis remained illicit. The use of the pre-existing programme designed for Randall became a method through which AIDS patients could gain access to an otherwise illicit substance and a compassionate access programme was utilised for AIDS patients. But the programme was a slight concession rather than a right. It had limited coverage of patient demand, was subject to sudden closure and was not a change to federal law. The programme became so popular for AIDS sufferers that it was closed in 1991, apparently due to the large numbers of subscriptions and fears that it was sending the wrong message to the public.¹⁴ Booth argued that the fury at the closure of the programme led to further development of the grass roots movement to protect patients and to the development of 'buyers clubs' for alternative and illicit remedies.¹⁵ However, the use of cannabis as an anti-nausea drug used in relation to cancer chemotherapy had already provided an example of a medical use of cannabis, and one that could be transferred to AIDS treatment. Dronabinol (Marinol) was therefore made available for prescription for AIDS patients in 1992 in the US. Patients who were already receiving herbal cannabis were allowed to continue but those who were in the process of being placed onto the compassionate programmes were provided with Marinol which enabled the US government to argue that smoked herbal cannabis for medical purposes was obsolete.¹⁶

Cannabis, multiple sclerosis and the patient perspective in the UK 1992-2007

Pressure from HIV/AIDS activists was relevant in the UK but it was not this activism that led to a change in the environment around cannabis. In the UK, it was a different disease, perhaps one considered more ‘respectable,’ in the form of MS and its associated patient demand which was to have a more influential and long-term impact on policy discussions and the development of cannabis medicine. A MS campaigner for access to cannabis commented, ‘*With AIDs – its your fault....so in this country the focus was on MS.*’¹⁷ In the UK a number of active self-help groups had been established to look after the interests of the approximate 85,000 MS sufferers. MS is a progressive, degenerative disease impacting on the brain and spinal cord nerves. Orthodox therapies included baclofen (Kemstro) and diazepam (Valium) for the treatment of muscle spasms and spasticity but their efficacy was limited and both had unpleasant side-effects. MS patients faced a variety of other medical symptoms for which there were no effective symptom control treatments, especially for pain. Some sufferers, often previously law-abiding citizens, found they could self-treat with cannabis either in the smoked or oral form.

This type of self help through ‘kitchen physic’ had yielded much anecdotal evidence of beneficial effects but there was limited scientific proof that cannabis was effective. In the early 1980s a few studies emerged in the US on the treatment of MS with cannabis. For instance, in 1981, DJ Petro and Ellenberger published a paper on the treatment of spasticity with the active principle delta-9 THC and in 1983 Clifford published the results of an open trial with eight patients given oral cannabis which found that it reduced tremors.¹⁸ In 1988 Ungerleider and colleagues carried out a study of twelve MS patients which, from the patient perspective, yielded significant improvements, but these improvements could not be backed up by objective observation by the medical staff.¹⁹ The numbers involved in the studies were small and results were ambivalent: only three double-blind placebo controlled studies involving more than one patient had been carried out and additionally some volunteers experienced a ‘high’, a reaction which was not considered acceptable in medical circles. These

experiments were promising leads but were not drug licensing exercises, and were not sufficiently large to provide proof of safety and efficacy which would be needed to take a drug through the regulatory processes. However, the discovery of the endogenous cannabinoid receptor system by the 1990s conferred legitimacy to the role of cannabis in the body and led to a snowballing of cannabis research. In terms of MS, articles appeared on the use of cannabis for fatigue, tremors, incontinence and pain. These publications, however, made little practical difference from the patient perspective but awareness was growing about patient self-medication of cannabis. A survey carried out by the MS Society revealed the widespread interest in cannabis amongst the Society's members.²⁰

A more educated and informed patient population was taking an increasingly active role in treatment options.²¹ Since the 1990s different types of self-help groups became vocal in pressuring for research on cannabis for MS. Three societies influenced the cannabis story and each brought a slightly different perspective and emphasis to advocacy on cannabis but together they provided real pressure for research.

The MS Society

Formed prior to the rapid development of many patient groups after the 1980s, the MS Society was the longest established patient association that advocated research on cannabis. The picture was complex. The shifting opinions of the MS Society towards cannabis reflected wider debates in medico-scientific and policy circles from the 1960s. Founded in 1953 it became a highly successful organisation in part due to the advantages that chronic disease associations have with long-lived members and public support. By 2000 the MS Society had become the largest charity for MS in the UK with 55,000 members, 35,000 of whom suffered from MS. It had become the major funder of medical research into MS in the UK with a funding commitment of more than eleven million pounds.²² The Society mingled lay and medical membership, and had its own research scientists and science advisers. It had two major aims: to support patients with MS and their families and to support research into the potential elimination of MS. Cannabis became of interest in the 1990s. MS policy was that if cannabinoid-based

medicine proved safe and effective in clinical trials then it should be made available to patients through the NHS. The Society stipulated that research should be vigorously pursued and that cannabis had to be judged according to similar criteria which applied to the assessment of any proposal for a new drug therapy and normal standards for quality, safety and efficacy. During the 1990s the Society became involved in funding a number of clinical trials. Its policy was not to recommend the use of herbal cannabis prior to clinical trials, though it did urge authorities to deal sympathetically with people who self-medicated with cannabis.

The MS Trust

The MS Trust was set up in 1993 by Jill Holt and Chris Jones both of whom had personal experience of MS. They had previously been involved with Action and Research into MS (ARMS) an organisation which had been active since 1974 to make applied research into MS a priority. ARMS closed in 1993 leaving a dearth of money for its research programme. Holt and Jones purchased the ARMS trading company and aimed to find the money to continue the research programme. They argued that applied research remained underfunded, information for the newly diagnosed was inadequate, the image of MS remained poor and that NHS services were limited. A small charitable trust was established with two MS researchers, and financial guidance. The Trust aimed to provide information, education, patient support and research funding. Clinicians described the Trust as '*a breath of fresh air*' in their willingness to fund, though their funding ability was very limited.²³ The MS Trust was more research driven than the MS Society but within this cannabis was merely one aspect of research.

The Alliance for Cannabis Therapeutics, (ACT)

In contrast to the MS Society and the MS Trust, the Alliance for Cannabis Therapeutics was created purely for the purpose to campaign for access to, and research into cannabis, mainly on MS but also for other applications. ACT was set up by Clare Hodges (Claire Brice), an MS sufferer, in 1992 at a time when many advocacy groups were developing.²⁴ ACT was based on the US Alliance for Cannabis Therapeutics,

which had a long established tradition of campaigns for medical access. ACT in the UK was created as a single-issue, single activity, self-help group for medical cannabis users to campaign specifically for research into cannabis and access to it on the NHS. Hodges suffered from spasticity, loss of sensation, bladder problems, nausea and loss of appetite. Nine years of orthodox medicine had provided limited sustained relief and many unpleasant side-effects. After reading about the use of cannabis in the *American Medical Journal* she tried smoking cannabis and found that while it did not cure the problem, it alleviated some symptoms including bladder problems, pain, and sickness.²⁵ She remembered,

*As I was a middle-class mother of two young children I had a bit of problem obtaining cannabis...eventually I found someone who helped me get some... When I did try cannabis the physical relief was almost immediate. ...I was comfortable with my body for the first time in years.*²⁶

Wood has argued that patient associations are largely a middle class activity and Clare Hodges fitted into this mould, and this perhaps worked to her advantage and brought a not so respectable activity into a 'respectable' setting.²⁷ She began to cultivate, smoke, and ingest herbal cannabis. With the introduction of nabilone she hoped to find a legal method of treatment, but instead found unpleasant side-effects, and that it failed to produce the beneficial effects of herbal cannabis. With the failure from the patient's perspective of the licit cannabis-based drug Hodges felt herself forced to revert to herbal cannabis. Her neurologist in 1992 put her in touch with others who were self-medicating with herbal cannabis and they decided to form a group to campaign for more research and provide information to sufferers and the public about medical cannabis issues. Hodges explained her motivation. "*I found out it was not just me... so I raised awareness and let people know about it...to let people know it helps.*"²⁸ Use of cannabis, however, posed problems from two points of view: first the threat of prosecution; and second a the lack of quality control and unknown dosage.²⁹

Since its formation, the ACT has aimed to encourage research into medical preparations of '*natural cannabis*' and for these therapies to be made available on a doctor's prescription while research was ongoing. Hodges recalled later,

We are not campaigning for the general legalization of cannabis. Indeed even if cannabis were legalized we would still be campaigning as we think seriously ill people should get their medication from their doctor and not have to provide it for themselves. Similarly the objectives of the ACT would not necessitate cannabis being legalized. Preparations of cannabis could be available for medical use whilst still being illegal as is the case for diamorphine /heroin.³⁰

ACT argued that herbal cannabis had a long usage, was safe and available. It went a step further than the MS Society and argued that patients needed immediate relief not help at some undefined point in the future. In the interim ACT demanded that herbal cannabis should be made available to patients. These three societies each with different backgrounds and variant aims nonetheless significantly contributed to the process of re-medicalization.

An important aspect of these patient associations lay in their ability to provide an interface between the patient view and researchers, thus drawing the lay and professional spheres closer together. Not all self-help patient associations were involved in educating and interacting with health professionals but these were important activities of the patient groups associated with cannabis and MS.³¹ What was more unusual was the existence of the patient experience and knowledge of a botanical substance which they felt could help but which was illegal. The groups were able to filter these experiences through to the science field. ACT developed close connections with scientists and the medical profession and was able to provide laboratory scientists with access to patient perspectives. Clare Hodges described the membership of ACT as a loose affiliation of patients, including those with spinal injuries and cancer, doctors, hospital consultants, and health workers.³² Its role as an interface between patients and doctors meant that it helped research to take place. For the scientists working on cannabis-based products the patient association provided a ready pool of patients, many of whom were actively interested in the research. ACT worked with Pertwee at Aberdeen University on a project on the perceived effects of smoked cannabis on patients with MS. ACT assisted by distributing a questionnaire and providing access to users. The links to the US ACT provided access to American users.³³ Similarly interactions were initiated with clinicians. Hodges developed links with an anaesthetist

Dr William Notcutt who was carrying out work on nabilone for pain. Through this relationship Hodges was able to obtain nabilone on a named-patient basis licitly rather than having to resort to the black market. Not many doctors were able or willing to prescribe nabilone on a named-patient basis and most patients were left to their own devices and in some cases turned to herbal cannabis. Hodges explained some of the difficulties involved in sourcing cannabis.

You can't get it from the doctor. There are only a handful of doctors that can do it. Others get it illegally from the black market but people are scared. They wrote to ACT asking where can we get it? Most people just don't know where to get cannabis.³⁴

Patient-doctor relationships provided a conduit for the patient perspective to reach the medical establishment. This was particularly important over the issue of the unsatisfactory nature of nabilone in comparison to herbal cannabis. Hodges described her attempt to move to the licit nabilone and stay off the illicit cannabis.

I had just been prescribed nabilone....I took this for four nights but it made me confused and clumsy. I persevered hoping it might be a substitute, but it wasn't.³⁵

The evidence base for the use of cannabis in MS was lacking, as was research into the most effective form of cannabis. For both patients and clinicians it became clear that research was needed on other cannabis-based products most notably herbal extracts rather than a single chemical entity like nabilone.

Interactions between laboratory scientists and the MS Society partially contributed to a breakthrough in scientific knowledge about the role cannabis could play in MS treatment. By the late 1990s, the MS Society had become interested in cannabis. This was important because the Society was an influential player. The Society described its role,

One of the MS Society's main objectives is to promote and fund MS research. We fund scientific and applied research in order to make the maximum impact on MS, and the quality of life of people affected by MS. Our fundraisers work hard to pump around two million pounds into research each year.³⁶

In this search for treatments cannabis was merely one treatment option for the MS Society and one with serious implications.

The Society placed emphasis on a respectable image and this image needed to be maintained especially if it was to deal with an illicit substance. This was achieved by maintaining a disassociation from legalization campaigns or demands for access to cannabis prior to clinical trials. Dr Layward, an immunologist at the MS Society, who had moved from academia to the charity sector and who had previously worked at the AIDS charity, the Terrence Higgins Trust, explained some of the initial concerns about an involvement with cannabis.

*Legalize Cannabis was the only strongly campaigning group at the time and we did not want be involved in the issue of legalization of an illegal substance.*³⁷

Legalization campaigns were re-emerging in the 1990s.³⁸ The MS Society was keen not to be associated with this type of campaigning. It had been cautious about cannabis research and refused to fund trials in the early 1990s.³⁹ The history of the MS Society provides some clues into its attitudes towards cannabis and its initial reluctance to be involved in related research. The early history of the Society showed that the Society's initial remit did not cover the sponsorship of scientific research mainly because of the antipathy of the medical establishment towards lay involvement.⁴⁰ By the late 1950s, the Society had changed its position on funding basic science research, but this changed focus led to disagreements over the allocation of scarce resources. The dilemma was that on the one hand, the Society called for patience in waiting for effective therapies implying they were imminent, but on the other hand indicated that there was much research still to be carried out. Attention was directed into understanding the disease, finding a cure and the elimination of the condition rather than treatment and care. But with no cure in sight, the Society was forced to take a greater interest in the alleviation of symptoms. Their image was crucial to their choice and timing of funding options. Writers on the early history of the Society have argued that it was the social background of the Society's founding members and, in particular, its ties to neurology that made respectability especially important to the MS Society.⁴¹ The Society's network and

support base meant that it was very much positioned on the side of orthodox medicine. What is seen as orthodox or respectable however is part of the wider debate over orthodox versus alternative medicine. The Society placed great importance in its early days upon remaining orthodox and ignoring fringe medicine and the need to be against *'new, untried methods of treatment.'*⁴² It received a constant stream of letters on alternative treatments and the Society saw MS as a disease that attracted a great deal of quackery and many extravagant claims of therapies. In relation to MS research and treatments *'being respectable meant a great deal.'*⁴³

The Society's membership upset by the lack of available effective treatments started to look for alternatives. Cannabis research whilst by no means mainstream had become more acceptable. As time went on cannabis-based therapies could no longer be ignored and in the 1990s a new Chief Executive, Peter Cardy, initiated a review of the attitudes of the membership. An ex-MS Society scientist remembered his interest.

*He took it upon himself to go out and talk to MS people a lot before he decided what to do....he said this is what I'm hearing.*⁴⁴

Cardy asked Dr Lorna Layward to investigate the potential of cannabis. She explained later her initial response to Cardy's request,

*Talking to people with MS is where this story starts. One of the early things the Chief Executive said to me was, "Is there anything in this cannabis story?" and I was incredibly reluctant.....my perception was that I did not want to get involved in legalization but wanted to focus on scientific evidence.*⁴⁵

But patient perspectives began to cut across these concerns. Dr Layward described the impact of the patient experience on her own attitudes after carrying out a survey on MS Society members and their reactions to cannabis, *'It is only when I started to speak to people with MS that I started to change my mind.'*⁴⁶ Layward never forgot one patient's response,

*I remember distinctly a comment.....He/she said, 'Bugger research, one puff and I can straighten my leg.'*⁴⁷

With these patient voices filtering through to the leadership of the Society, the Society began to take a different approach to cannabis.⁴⁸

The Society applied pressure to shift anecdotal evidence onto a scientific footing. The discovery of the ECRS had given legitimacy to anecdotal reports of cannabis' medical usage but proof was needed of its value in specific applications such as MS. Layward believed that evidence of cannabis' effect on MS was required to provide the justification for clinical trials. When investigating existent research on cannabis and MS she made links with Pertwee, and Dr David Baker at the Institute of Neurology who though not working on cannabis, was working on long-term tolerization in animal models.⁴⁹ Layward asked Dr Baker to carry out systematic research on the effects of cannabis on MS and she put him in touch with Pertwee.⁵⁰ Layward described how a new project came about.

*If we were going to do anything about this in terms of clinical trials, we needed some sort of evidence.On the back of a fag packet in a pub over a drink we cooked this up.*⁵¹

It took about six to seven months to develop equipment to measure the effect but the project results showed cannabis had a significant impact on tremors in mice, similar to those experienced in MS.⁵² The experiment revealed the validity of the patient experience. Layward described the impact,

*It showed for the first time objectively that cannabinoids could do what people with MS were telling us. What we had demonstrated was.... 'one puff and I can straighten my leg'.*⁵³

The results were fed through to emerging discussion on potential clinical trials and were published later on the front page of *Nature* and this had a worldwide impact and gained much positive reportage in the media in the UK.⁵⁴ This research was important because as Baker recalled it '*started to put biology behind the patient experience.*'⁵⁵ Laboratory research was a start but for patients to benefit changes had proven in the clinic.

Patient need led to different approaches to the situation by the different societies.

The MS Society was keen to push for clinical trials to go ahead as the only method for getting cannabis-based drugs to their members. ACT was keen on clinical trials but recognised that there would be a huge time lag from clinical trials to the development of a medicine and it preferred to pressure for access to herbal cannabis in the interim. Hodges described the pressure for faster solutions.

*We want to see the problem addressed now as well as the research. You can do the two in conjunction.*⁵⁶

The MS Society explained the desire for a more cautious approach in 1997.

*Any proposal for therapy has to conform to stringent medical standards.... Unless and until such trials are undertaken and a therapeutic benefit is demonstrated the MS Society would not support the prescription of cannabis for people with MS.*⁵⁷

With their concern for the long term, the MS Society echoed Paton's precautionary outlook, and argued that since MS was a long-term illness any drug had to be effective and safe over the long-term. In not advocating the use of cannabis, and not advocating any change to the law surrounding cannabis, they perceived themselves able to maintain their respectability and therefore their influence on the policy and medical environment.

Clinical trials therefore became of critical importance for patient associations and especially the MS Society. Layward described the importance of trials,

*We had been aware of the anecdotal evidence of the benefits of cannabis for some time, but strongly believed that trials were essential to rigorously test the effectiveness of the drug and to develop safe and easy methods of use.*⁵⁸

Key to the initiation of the trials was the relationship between the MS Society and Tony Moffat, the Chief Scientist at the Royal Pharmaceutical Society. Layward explained the convergence of interest in clinical trials by patient associations and professional bodies.

*We both had the same sort of viewpoint. Not interested in legalization... what we were interested in, was there any medicinal use? That marriage... that relationship was absolutely pivotal to making all of this happen.*⁵⁹

The MS Society joined forces with the Royal Pharmaceutical Society and the BMA and, as is discussed in chapter seven, jointly organised an influential conference in 1997 for scientists, patients, neurologists and industry representatives on the subject of clinical trials.⁶⁰ Nervous of the press response, and the risk to the reputation of the Society, the Society was still wary, but it seemed that the time was right for trials to proceed. Layward described the coalesce of factors that allowed research to go forward.

We were pushing a time when there was a lot of resistance but over the coming year the resistance fell away. There was the discovery of the cannabis receptor system, MS and HIV patients talking about cannabis in terms of making them feel better...there was a clamouring from different groups of people and anaesthetists were interested in pain relief.⁶¹

The symposium was critical in that it drew scientists, patients and most importantly funders together and focused their attention in the provision of protocols for trials on MS and pain. Importantly, it drew industry attention.

ACT, in particular, actively sought out the pharmaceutical industry in an attempt to encourage the production of legal of cannabis therapies. It contacted several companies to no avail as cannabis therapies were seen as too controversial and not worth the investment. Hodges recalled,

One company which I cannot name...took it quite a long way ...and told me in confidence that it was too controversial, the scheduling was too difficult it just was not worth the investment. They took it seriously but they did not want to do it.....at the Royal Pharmaceutical Society last summer I met a man who is an ex-chairman of a pharmaceutical company and he had tried to get a Home Office licence and had preliminary discussions with them four years ago and he had been advised not to go ahead. Recently, I approached him and suggested that he had another go and he tried again.⁶²

The meetings organised by the Royal Pharmaceutical Society were important because they allowed for interactions with Geoffrey Guy and other stakeholders. But for industry involvement to go forward it required the approval of the Home Office and the patient groups were important in placing pressure on government.

The MS Society and ACT sought to bring the patient perspective closer to policy makers. They did this in a mixture of ways. They developed relationships with professional bodies including the British Medical Association, (BMA). As discussed in chapter seven, influential reports on therapeutic cannabis such as that by the BMA that emerged in the 1990s absorbed evidence given by the ACT and the MS Society.⁶³ Such reports by professional bodies contributed to a change in the policy environment around cannabis that was taking place in 1997. ACT was especially effective at keeping the issue high on everyone's agenda through the media. In commenting on the role and significance of ACT, Layward reflected on the importance of this type of activism in applying pressure for change.

*We couldn't get anywhere without those sorts of groups for keeping the agenda high, for speaking to the press.*⁶⁴

Indeed press responses were largely positive towards medical cannabis use and it was a popular human interest topic, helping to keep the issue on the agenda.⁶⁵ Hodges described the reaction to her first newspaper article on cannabis and her advocacy.

*Three hundred individuals wrote in about how much they had benefited from it. All grist to the mill, wasn't just me. Doesn't take long for it to get around.. The press very much like running stories about it because most people in the press use it and they liked stories like that.*⁶⁶

This publicity highlighted the problems of prosecuting patients for trying to alleviate their symptoms and increased public support for their cause.

Links between activist groups and the policy community were important during this period.⁶⁷ Whilst the MS groups were by no means so closely associated with a 'network of influence' as organisations like Action on Smoking and Health (ASH) they did make a contribution to the policy environment. ACT, in particular, began to lobby government. It organised delegations which included MPs, scientists and clinicians, to the Department of Health in 1994 and 1997 and these stressed the need for medical preparations of herbal cannabis to be made available for research and they argued that in the interim that prescription on a named-patient basis should be

available.⁶⁸ Hodges courted the support of sympathetic MPs such as Paul Flynn and MS groups were important in the All Party Parliamentary Group for MS. The group was made up of MPs and peers with a specific interest in MS, and was established in 1997 to promote the interests of people affected by MS. This interaction at the heart of government enabled the patient associations to raise the profile of the MS issue and, within that, the need for clinical trials.⁶⁹

Patient groups also contributed to parliamentary expert committees. The MS Society and ACT were the only two self-help groups invited to present evidence for the House of Lords Committee on therapeutic cannabis during the late 1990s. Their evidence provided the opportunity to place the patient perspective before the House of Lords and generate more public awareness of the issues. They raised concerns over the lack of treatments, the importance of clinical trials and the form of the drug to be trialled.⁷⁰ ACT campaigned additionally for the need for access to cannabis whilst trials were developed. The MS Society through the evidence of Layward and Mrs Carlyle, the information and education manager, pressured for the development of clinical trials, raising awareness of the nature of MS and its potential impact on clinical trial evidence. Whilst they accepted many of the points made by Clare Hodges they made it clear they were not prepared to accept anecdotal evidence, nor to push for interim access to herbal cannabis. They argued that clinical trial evidence for the efficacy of the new beta-interferon treatment was sufficient to justify prescription and in the absence of comparative evidence for cannabis the Society could not support its use in clinical practice. However, they emphasised it was *'essential that further research is taken'* and steadfastly pressed the case for clinical trials. However, they were concerned that clinical trials, because of the nature of the disease, and the substance being tested, would pose complications. A large section of their evidence to the House of Lords Committee was given over to the methodology of potential clinical trials, predicting many of the problems that emerged later when trials were carried out. In contrast to the initial policy of the Society, they argued that disincentives to research were financial and attitudinal rather than legal and that they were happy to fund research to some degree.⁷¹

Activists in giving evidence to the expert committees provided an effective conduit between grass-roots advocacy, practical knowledge of using the drugs, and policy-makers and lawmakers and helped to shape the form of the debate in a way that had not occurred in the closed expert discussions of the 1970s. Differences of opinion existed on the importance of the House of Lords Report in this process. Whilst some such as Philip Robson have argued that it was critical in allowing research to go forward,⁷² Layward argued that the trials would have gone ahead without the report and rather the report reflected the existent groundswell.

*We carried on anyway... they came up with what we were doing anyway.... it was because there was a groundswell. Without it, it still would have happened.*⁷³

The ability of activist groups to potentially provide funding for clinical trials was particularly attractive to GW Pharmaceuticals as a newly established company when no government funds were forthcoming. Geoffrey Guy, the founder of GW Pharmaceuticals appeared hopeful when he gave evidence to the House of Lords Committee in 1997.

*I think also that the new research here, which is very much patient demand led will be accompanied by funding for research programmes... the MS Society has already said they would support clinical trials. ... As yet there seems no prospect of any funding from government.*⁷⁴

Though no funding came to industry as the MS Society ploughed money into the proof of principle trials, their advocacy was significant in influencing industry research in the direction of MS. Robson of GW explained the impact.

*MS is a major awareness group in this country. So, at the beginning, a focus on MS was sensible.*⁷⁵

It was also sensible for marketing reasons. Paton had previously argued that cannabis-based medicines did not compete favourably with other available medicines but in MS it was hoped that 'CBME (cannabis-based medicine extract) would not merely be equal in efficacy to standard drugs but rather offer tangible advantages in a difficult clinical context.'⁷⁶

Activists with so much staked on the outcome of research were keen to influence its direction. One area of contention was the debate over the form of cannabis to be used, for instance, the use of herbal cannabis or drugs derived from single, active synthetic principles. Nabilone had been licensed for treatment in cancer chemotherapy but it could be prescribed for MS patients. MS patients with the experience of self-treating with herbal cannabis found, as had been the case earlier with HIV/AIDS patients, that the synthetic THC legal drugs appeared inferior in terms of their efficacy and side-effects. This experience was noted in the House of Lords Report.

Nabilone does not seem to be an effective substitute for cannabis used therapeutically....all those who have taken both nabilone and natural cannabis say that cannabis is more effective and easier to control.⁷⁷

ACT, in particular, campaigned for patient use and the study of herbal cannabis.⁷⁸ The MS Society, too, had concerns over the form of cannabis trialled. The Society argued that there might be many useful cannabinoids within cannabis or an interplay between cannabinoids. They pressured for a trial on herbal cannabis, and another on specific cannabinoids. They were keen to look for cannabinoids which lacked the psychoactive element. In its presentation to the House of Lords committee the Society argued for different arms to the trials.

While a single cannabinoid which can be produced to a consistent standard may seem attractive, with a least sixty six cannabinoids to choose from this may be impractical. In addition there may be many individual cannabinoids which are beneficial with a possibility that an interplay between cannabinoids which possess a beneficial effect. Trials could take place in two phases. The first phase could consist of a trial of the whole cannabis..... this would allow some results to become available at a reasonably early stage. The next phase could consist of trials of special compounds.⁷⁹

Pressure originating from the practical knowledge and experience of user activists led to questions over the effectiveness of single extracts like nabilone and forced re-consideration of herbal cannabis.

Patient associations were involved in discussions over the route of administration. Members of the MS Society, in a survey had expressed concern over the effect of

smoking on their general health and the Society doubted that any drug administered via smoking was likely to pass through the regulatory mechanisms. In this they concurred with established opinion. ACT offered a different perspective.

With a disease so unpredictable, self-education seems more helpful than treatment with a regular dose of a fixed strength... People gain from treating themselves...this probably explains why most people choose to smoke cannabis.... The advantages in taking cannabis via the lungs is that the effects are much quicker and therefore easier to regulate.⁸⁰

Smoked cannabis was not however one of the ACT's demands and the scientific community was clearly against trialling any form of smoking. But while patient groups waited for trials to go ahead, they continued to campaign for compassionate treatment of cannabis users. An MS Society spokesman was reported by the BBC as pressuring for the end of criminalisation of patients who used cannabis.

We want to see trials advance as quickly as possible...in the meantime the reality is that there are people who suffer severe disability and painful symptoms for whom the only way of easing the pain is smoking or eating cannabis.⁸¹

Activists could claim some credit for the large-scale clinical trials that took place on cannabis for MS after 2000.⁸² Chapter eight discusses the development and outcomes of the clinical trials in-depth but with specific reference to advocacy, activists faced some disappointments with the results of the major clinical trials that emerged. In essence the results of the trials were inconclusive and failed to produce the evidence-based proofs sought by the clinicians. Yet the majority of patients taking part appeared to find benefits to their lifestyles. The problem, in part, centred on the method of administration, which from the patient perspective, was an inferior model. Dr Layward suggested later that the trials were compromised in some sense from the start, 'The protocols got compromised so much. What, you would like to do, is often what you can't do in patients.'⁸³

Unusually patients had practical experience of alternative methods. As it was not possible to test these, investigations took place on more 'acceptable' delivery methods

but from the patient perspective these seemed to lack the effectiveness of smoked cannabis. Patient associations questioned the nature of evidence and the role of the patient perspective within clinical trials assessment when clinical trial results were published in 2003.⁸⁴ Researchers found that cannabis had no significant effect on the key symptom measurement of muscle spasticity as measured by an independent assessment of clinical spasticity known as the Ashworth scale. The MS Society raised the question of how patient perspectives were weighed as evidence, and they argued that something of a small statistical value could radically change a patient's life.

*The results of this large trial show the difficulty in assessing treatments for a variable and fluctuating condition like MS. Current methods of measurement do not always detect significant benefits patients may feel. Around two-thirds of those on the cannabis-derived medicines felt their spasticity was improved by them, even though that could not be shown clinically. More people on the drugs found relief from other very distressing symptoms like pain, spasm and sleeping problems than those taking a placebo. These improvements to quality of life can make a significant difference to people with MS, whose choice of treatments is very limited.*⁸⁵

It was clearly feared that the patient perspective was lost in the data.

The MS Society was particularly keen to bring the patient perspective to the notice of medical advisory bodies. The MS Society, along with other stakeholders including the manufacturers of the drugs under trial and health professionals' organizations, made submissions to the National Institute for Health and Clinical Excellence (NICE). NICE was the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health through health technologies. The MS Society urged NICE not to take a too narrow a view of the subject.

*We urge NICE to take full account of the views of people affected by MS. People with MS call for members of NICE to shadow them for a day: to 'walk in their shoes'. Only with this information do they feel that it is possible to understand the true value of these products.*⁸⁶

In particular the MS Society highlighted concerns over existent outcome measures.

Even if the trials show that the overall clinical benefits of the drug are small the impact this may have on quality of life for individuals should not be underestimated. We hope the trials will have data from the use of robust quality of life measures that have been developed and validated by people with MS. Clinically based outcome measures alone may not be sensitive enough to detect the changes that are important to people with MS.⁸⁷

They were keen for NICE to consider individual rather than universal benefits.

The data may be 'muddied' by the variability in people's experience of symptoms of MS and the normal variation in people's response to cannabinoids. It is likely that some people will receive symptom relief, although not everyone will benefit. We are concerned that these significant improvements should not be 'lost' in the background noise.⁸⁸

The Society advanced their case on more than medical grounds. They pushed the legality issue and argued that the production of a legal medicine would provide a clear split between recreational and medical use and remove the risk of self-treating patients becoming entangled in the criminal justice system.

We are aware that some people with MS are already benefiting from the use of cannabis, but by being forced to engage in illegal activity are experiencing great distress and fear. People have no choice but to put their health, personal safety and careers at risk in order to obtain some relief of their symptoms. Others deny themselves symptom relief because they fear prosecution. Offering cannabinoid-based treatments via the NHS will provide a much valued opportunity to use the drug in a safe and trusted environment.⁸⁹

The submission highlighted the continued connection between medical use and criminalization, and the implication that this held for some patients: that the government position left them no option other than to deal with drug dealers.

And that's what the Government are making you do... deal with drug dealers who could be ripping you off or anything.⁹⁰

It highlighted some patients' perceptions that discussion on cannabis medicines was centred on political not scientific agendas.

People with MS are concerned that the political issues around recreational use of cannabis may unfairly influence a decision about cannabinoid-based medicines. If a plant was discovered in the rainforest, then they probably would be called a miracle cure you know. It wouldn't have all this political baggage behind it.⁹¹

The patient perspective had helped take the process of re-medicalization so far. It had lobbied and pressured for research and access. Clinical trials had taken place but there remained a long time lag before any change would be seen from the patient perspective.

Patient activism began to tail off after the turn of the millennium. ACT, for instance, began to cut back on its campaigning. Hodges explained the problems of advocacy faced by MS patients.

People with MS are weary and ill and haven't got the energy to campaign. People with AIDS are often very active and angry and young and otherwise healthy. With MS you find out quite young that that's it and you lose the will to fight for yourself. There's not much you can do about it.⁹²

The MS Society had a structured organisation, including expert scientists able to campaign on behalf of its members, but it had other interests to campaign for especially whilst clinical trials, both proof of principle and industrial, were ongoing. Whilst Sativex made its way through the regulatory process it was made available on a named-patient basis. At conferences, patients appeared to give positive reports of Sativex, but to what extent were these 'tame patients'?⁹³ In 2009, at a witness seminar on the medical use of cannabis, the experienced activist, Hodges, queried the long-term side effects of cannabis and the impact of Sativex. Was longer term lay knowledge leading to an alteration in the patient perspective? It remains open as to what impact the introduction of Sativex will have on medical cannabis activism. As far as the membership of these societies was concerned perhaps not much had changed but through their lay knowledge and advocacy the process of re-medicalization had been taken forward.

Conclusion

Lay knowledge and patient advocacy was critical in the process of re-medicalization. Medical advocacy of cannabis by patients became increasingly significant, altering both its own approach, and contributing to the changing direction of re-medicalisation.

In the 1960s and 1970s pressure groups campaigned for the legalization of cannabis as part of a lifestyle choice. As part of their arguments these pressure groups raised the issue of medical cannabis which had arisen through the wider use of cannabis recreationally, but with their main focus on the politically contentious issue of legalization for recreational use they had limited policy impact. As lay knowledge around cannabis' medical properties increased advocacy based purely on medical arguments became prominent especially in the US in the late 1970s and early 1980s. This resulted in the successful legal argument of medical necessity for the use of cannabis and the original development of patient associations for glaucoma and the initial development of compassionate access. These campaigns combined with developments in the scientific field provided much greater legitimacy for cannabis' medical use. The AIDS crisis then propelled the issue forward and achieved some changes with, for example, the expansion of compassionate access programmes but it did not lead to lasting changes in policy. These arguments filtered through to the UK, where they stimulated the development of equivalent UK Societies, but in the 1990s pressure emerged from a different quarter. In the UK the MS patient associations, in particular ACT (UK) and the MS Society, became examples of very active patient associations which interlinked with scientific and policy spheres. These societies had some differences of opinion and some different approaches but their combined advocacy provided a respectable face to medical cannabis use. Patients had limited power in their own right, their power lay in their knowledge and their ability to place pressure on other actors in the re-medicalization process especially after their experience had been validated to some extent by the discovery of cannabis' mode of action. They were successful in this and became interlinked and inseparable from the other main actors including, industry, media and clinicians, professional bodies, and government. Some patients had firsthand experience of the herbal product and or the derivatives of cannabis

and so they were able to have an impact upon not only the initiation of research but also its direction. They were the ones that brought herbal cannabis to the fore demanding a product much more closely related to their own experience than the synthetic single active principles which had previously made it to market. They also affected the policy environment, especially as they pulled cannabis use into a more 'respectable' framework and by keeping the issue in the minds of the press and public they created a groundswell of support for the issue. Through lobbying, parliamentary discussions and submissions to key reports of the period they kept the issue high on the political and scientific agenda and encouraged the shift from anecdotal lay knowledge to the facilitation of evidence-based knowledge with the initiation and development of clinical trials, both proof of principle and industrial. Funding was ploughed into the arena and fears over the loss of the patient perspective in clinical trials led to the reinvestigation of clinical trial methodology and the development of more subtle outcome measures which might lead to successful outcomes in future trials.

Though lay knowledge and advocacy had an important impact on the process of re-medicalization how much changed from the patient perspective is limited. The production of a licit cannabis-based drug has often appeared to be almost within reach but never quite there. The following chapters consider the emergence of clinical trials and the process which took cannabis-based drugs through the licensing procedures.

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Chapter Seven

Establishing therapeutic cannabis: The role of expert advice in the process of the re-medicalization of cannabis, 1997-2005

In analyzing the process of re-medicalization of cannabis this thesis has examined the science-policy interchange through a study of governmental expert committees and reports of professional bodies. Whilst an earlier chapter focused on the private committee discussions of the ACMD in the 1970s and 1980s this chapter explores the public reports on therapeutic cannabis that emerged from 1997 onwards. These reports of the 1990s focused specifically on the therapeutic uses of cannabis. They drew clear distinctions between the role of cannabis as a medicine and concerns over its recreational use. The reports contributed significantly to the legitimatization of medical cannabis and to a shift in attitude towards cannabis, which was downgraded in 2004 from Class B to Class C under the Misuse of Drugs Act 1971. The chapter begins with a look at the initiation and impact of the British Medical Association's (BMA) report on therapeutic cannabis in 1997 that cited unmet medical need that could be met by derivatives of cannabis. The House of Lords Science and Technology Committee report followed a year later and called for research on herbal cannabis as well as its derivatives. These reports pressed for clinical trials, industry involvement and a re-consideration of policy on cannabis. This chapter overlaps in time with chapters five and six but demonstrates how industrial interests and patient concerns discussed in those chapters were turned to put to practical effect. The chapter continues by looking at how pressure mounted for medical use and the rescheduling of cannabis, via the Runciman Report of 1999 and the House of Lords follow-up report of 2001. The chapter concludes with the decision to downgrade cannabis from Class B to a Class C drug.

Cannabis in Context: Changing attitudes to cannabis in the 1990s

Before analyzing the expert advice of this later period it is worth considering the wider environment surrounding cannabis in the late 1990s. In the 1990s 'cautioning' was

taking over from prosecution and the concept of ‘harm reduction’ was given greater acknowledgement in policy.¹ The government deemed that public opinion was more tolerant towards cannabis. Questions in the House of Commons increased over the issue of therapeutic cannabis for sufferers of MS and cancer. MPs such as Paul Flynn, MP for Newport West, and a former industrial chemist, pressured in parliament for legal medical use of cannabis and delegations were received by government on the therapeutic use of cannabis. Emphasis was placed onto the outcomes of the clinical trials before any modification to the MDA would be considered.² The Department of Health at the request of the ACMD had commissioned a series of unpublished literature reviews on cannabis in 1996.³ One on the clinical and pharmaceutical aspects of cannabis was by Professor Heather Ashton, Professor of Clinical Psychopharmacology at the University of Newcastle upon Tyne. A second on the psychological and psychiatric aspects was written by Dr Andrew Johns, from the Institute of Psychiatry. The third on the therapeutic aspects of cannabis and cannabinoids was produced by Dr Phillip Robson, Consultant Psychiatrist and Senior Clinical Lecturer, at Oxford University who went on to become Medical Director for GW Pharmaceuticals.⁴ Paul Flynn, who had campaigned for access to cannabis for medical reasons, announced his intention to ask the All-Party Drugs Misuse Group to back new research to establish the risks and benefits of cannabis with the goal of directing parliamentary opinion in favour of reform. 1997 marked a watershed for cannabis as a therapeutic. Initially, the incoming New Labour government wished to appear to take a tough stance on the drugs issue, and appointed a US style ‘Drugs Tsar’ Keith Hellawell, a former chief constable of West Yorkshire and a liberal deputy, Mike Trace, formerly of the Rehabilitation for Addicted Prisoners’ Trust. The incoming Home Secretary, Jack Straw, appeared adamantly opposed to cannabis decriminalization. But pressure was mounting for a re-evaluation of the situation. Popular support grew for decriminalization and public figures such as Paul McCartney, Richard Branson, and Anita Roddick backed a change in status. In more liberal sections of the media, cannabis and its legalization was viewed positively. The Independent on Sunday, under the editorship of Rosie Boycott launched the Decriminalise Cannabis Campaign, in September 1997 and declared that the campaign would continue, ‘until the law is changed and possession of marijuana for personal use is no longer an offence.’⁵ The medical use of cannabis focused

prominently and the paper reported that an anonymous poll taken of MPs revealed that 70 percent said that there was a case for allowing doctors the right to prescribe cannabis for medical purposes.⁶ Senior figures within the legal system called for a re-opening of the debate. The Lord Chief Justice, Lord Bingham, announced his support for open debate on the issue of legalization of cannabis in October 1997 and his comments were widely reported in the press. Some government members began to indicate a softer line. The Health Secretary, Frank Dobson, reportedly said that he would consider making medical cannabis legal, through a doctor's prescription, for sufferers of illnesses such as multiple sclerosis. In 1998, a ten year drug strategy was launched by government which argued that government resources should focus on drugs that caused the most harm such as heroin and cocaine.⁷

International agencies which had been more noted for their hostile approach to cannabis began to moderate their views to therapeutic cannabis in the 1990s. The WHO had been under pressure to review the literature on the health consequences of cannabis since the 1980s. It had established an Expert Group on Cannabis in 1993 and in December 1997 released the report, *Cannabis: health perspective and research agenda* aimed at policy-makers, and others concerned with public health.⁸ The report included a section on the therapeutic use of cannabis. It recognized that the role of derivatives had been established in the late 1970s and early 1980s and this acceptance began to impact on attitudes to herbal cannabis. Whilst not enthusiastic, the WHO considered what issues had to be overcome in order to study herbal cannabis.

The therapeutic uses of THC ...have led to discussion about the therapeutic potential of cannabis itself... To explore possible therapeutic uses... several scientific issues need to be considered...the standardization of cannabis preparations... the large number of patients which would be needed to study the comparative efficacy of smoking cannabis compared with other cannabinoids and other therapeutic agents, and the possibility of using alternative delivery systems which could avoid cannabis smoking.⁹

But the WHO remained concerned over the broader implications for drug control policy and possible adverse effects of cannabis, particularly mental health, but these were not considered to outweigh potential benefits and the report called for further research

both in the laboratory and in the clinic.¹⁰ The report received more publicity than had been expected as it turned out to be rather controversial, not for what was included, but for what was left out. Reports emerged in the media in 1998 that evidence had been suppressed after pressure was placed on the WHO by the UN International Drug Control Programme, which had been created in 1990 to improve the efficiency of the UN's drug control structure.¹¹ The material in question related to comparisons between cannabis and legal substances like tobacco and alcohol. The WHO was forced to issue a rebuttal, '*there was therefore no attempt to hide any information and the decision not to include such a comparison in the final report was based on scientific judgment and had nothing to do with political pressure.*'¹² The controversy highlighted tensions between the agencies and the problems posed for drug control by cannabis. The comparison between cannabis and alcohol and tobacco that had gained ground since the 1970s now raised more controversy than any endorsement of therapeutic cannabis and the issue of relative harms between licit and illicit drugs would be re-visited in domestic debates in the first decade of the twenty-first century.

In the UK concerns over the implementation of existing drug policy had increased: stricter control and an increased number of prosecutions seemed to have limited impact on use levels; the cost of policing was rising and the impact on civil liberties remained a concern. But fears also remained over the relationship between cannabis and mental health, especially in light of claims of increasing THC content, and the uncertainty of reactions to changes in policy by the media and public.¹³ Driven by these concerns between 1997 and 2004 professional bodies and expert committees began to study cannabis therapeutics and looked at ways to take forward the therapeutic use of both derivatives and herbal cannabis and they considered the question of the placement of cannabis within the drug control mechanisms.

The Role of Professional Bodies. The BMA Report: Therapeutic Uses of Cannabis 1997

*This Representative Body believes that certain additional cannabinoids should be legalized for wider medicinal use.*¹⁴ BMA Report 1997.

It was against this backdrop that the BMA released its ground-breaking report the *Therapeutic Uses of Cannabis*, and added an influential, professional medical voice to the debate. It endorsed medical applications for the constituents of cannabis and indicated that the law surrounding them should be modified.¹⁵ The BMA, the UK body which represented the medical profession had, from its inception in 1832, commented upon key issues and sought to influence public health legislation.¹⁶ The Association had an Annual Representatives Meeting, (ARM) which allowed members to debate motions and a Board of Science and Education, which acted as the interface between the profession, the government and the public. The Board established special working parties and steering groups and convened outside experts for specific scientific projects which had led to the publication of reports on a wide range of public issues, from the environmental risks of pesticides to drink-driving.¹⁷

A resolution was adopted at the ARM in 1994 that requested the Board of Science and Education to look at the relative risks of drugs of addiction, and advise on drug misusers who wanted to break their habit, drug misusers who wished to continue, and arrangements that did, or could, exist in the future for supplying drugs to either category of drug user. A third point was added to the resolution to consider the benefits or otherwise of decriminalization or legalization of some, or all, controlled drugs.¹⁸ Sarah Mars, who part authored the report, explained that this final request “*got tacked on at the end by one of the doctors at the BMA’s Annual Representative Meeting and it was agreed that they should do it.*”¹⁹ Legalization or decriminalization was a controversial area for the BMA to step into. The final report explained that the BMA had refined part three of the resolution to refer only to controlled drugs in relation to their ‘*therapeutic use, by patients under medical supervision, for particular medical conditions.*’ Cannabis was chosen because it was of ‘*wide public and professional interest.*’²⁰ In addition, cannabis therapeutics was noted as attracting increased interest in the light of the ‘*increasing acceptance of herbal medicine and ‘natural’ remedies.*’²¹ The report was published as a separate policy document to the larger and less well known BMA report *The Misuse of Drugs*.²² It was possibly a way to assuage the issue. Sarah Mars explained the reason for a separate report.

*The Secretariat did not want to touch that issue....The BMA is a very cautious organisation. They got round it by saying they would look into the therapeutic uses of cannabis as a fudgy way of tackling the last section.*²³

The BMA commissioned an external expert to produce a report on cannabis. Professor Roger Pertwee, with his experience on the pharmacology of cannabis was asked in the first instance. Pertwee discussed the pharmacology of cannabis including the newly discovered endocannabinoid receptor system and went on to make recommendations which included that patients with terminal illnesses should be allowed to smoke cannabis on compassionate grounds. The recommendations created controversy on several fronts: smoking; the use of a herbal product; and the potential press response.²⁴ Such reports were usually sent to two external expert referees whose comments were returned to the Secretariat who produced the final report. Pertwee's report was sent to Professor Heather Ashton. Concerned over the possibility of increased potency of herbal cannabis she suggested numerous changes. In light of her comments and her previous work, it was decided to abandon Pertwee's report and invite Ashton to write a more extensive report.²⁵

Others involved in the BMA report included Professor Jack Howell who was chair of the Board of Science and Education, but who had little involvement in its production, Vivienne Nathanson, Head of Professional Resources and Research Group, and Dr David Morgan, Head of the Science Department. Most of the writing was Ashton's work with contributions on some points from Pertwee; Dr Tony Moffat of the Pharmaceutical Society; Professor Patrick Wall, a pain specialist; and Sarah Mars. Clare Hodges of the ACT contributed on the patient experience, and Dr William Nottcutt, an anaesthetist, on his experiments with nabilone on pain and MS.

The report made eleven recommendations. In direct contrast to most previous reports on cannabis, it drew a distinction between medical use upon which the report was focused and recreational use of cannabis which was outside the remit. The impact of medical use on drug control policy was not considered relevant to their investigations.²⁶ The BMA report turned the previous situation on its head. Instead of the medical use of cannabis interfering with drug control policy, drug control policy was

interpreted as interfering with legitimate medical use. It argued that the WHO, should advise the CND to reschedule certain cannabinoids and that the Home Office should amend the Misuse of Drugs Act accordingly. It recognized that major amendments to international legislation were unlikely and recommended, instead that the government consider changing the Misuse of Drugs Act to allow the prescription of cannabinoids to patients with particular medical conditions that were not adequately treated and that a central registry be kept of the patients to follow-up effects over the long-term.

Selected areas of research were to be encouraged and the pharmaceutical industry was to be drawn into the process.

Pharmaceutical companies should undertake basic laboratory investigation and develop novel, cannabinoids analogues, and research on clinical indications for medical perscription should undertaken, especially for anti-emetics, MS spinal cord injury and spastic disorders and pain, epilepsy, glaucoma, stroke and immunological effects.²⁷

To alleviate hindrances and facilitate research the report indicated that the Regulations should be altered.

The regulation of cannabis and cannabinoids should be flexible to allow such compounds to be researched without a MDA licence issued by the Home Office.²⁸

The form and mode of delivery of cannabis remained important questions. The BMA placed emphasis on cannabinoids, rather than herbal products with unknown concentrations of cannabinoids.²⁹ Sarah Mars explained the cautious approach.

The culture of the BMA meant they felt more comfortable with that. They were uncomfortable with leaf forms. It didn't seem scientific.³⁰

The herbal product was not considered as it was the choice of recreational drug users and nor was the use of a 'leaf' or herbal forms considered acceptable within the context of mainstream medicine.

Critically, largely independent interests were drawn closer together with the aim of achieving a cannabis-based medicine. The BMA report helped to stimulate this process by urging all stakeholders to work together to develop clinical trials.

*The Clinical Cannabinoids Group, interested patient groups, pharmaceutical companies and the Department of Health should work together to encourage properly conducted clinical trials of cannabinoids alone, or, in combination and, or, in combination with other drugs.*³¹

Whilst new drugs were being developed the report urged that the police, courts and authorities should take account of medical reasons for unlawful use.

The report was released in November 1997 with a press release which was careful to draw a line between recreational and medical use, but which also drew attention to some of the more emotive issues of medical cannabis use.³²

*Therapeutic Uses of Cannabis draws a distinction between recreational misuse and using the drug to relieve pain. The report acknowledges that thousands of people resort to taking cannabis illegally...to ease their distressing symptoms.*³³

The report generated considerable attention and it had to be re-printed. It was widely covered in the media: most coverage was positive with headlines such as 'Doctors' support for cannabis.'³⁴ As government had feared some sections of the media, including the *Independent on Sunday* linked medical arguments to policy change and re-opened calls for decriminalization.

*Its appearance under the name of the BMA will give the findings added weight. It will increase pressure on the government following the launch of the Independent on Sunday's campaign for the decriminalisation of cannabis and the call by the Lord Chief Justice, Sir Thomas Bingham, for a debate on the issue.*³⁵

The Independent on Sunday used the report to add weight to decriminalization arguments and commented, 'The publication...of the BMA's report...will kill off the last arguments against the decriminalisation of the drug for medical use...' ³⁶ After the

release of the report, *the Independent on Sunday* convened a conference, *Cannabis: Should it be decriminalized?* which included speakers such as Professor John Strang, Director of Addiction Research, National Addiction Centre; Anita Roddick, Body Shop owner; Mike Goodman, Barrister, Director of Release; Professor Colin Blakemore, Chairman of the British Neuroscientific Association; and Nigel Evans, Conservative MP. No spokesperson from the Home Office or the BMA attended. Rosie Boycott drew attention to cannabis therapeutics in her opening speech.

A society ...that has denied a very benign drug to MS sufferers, to recreational users, and that has made people criminals. By choosing to stick to this... 'just say no' approach we have a wildly escalating drug problem.³⁷

During the conference frequent references were made to the BMA's conclusions on therapeutic use. Austin Mitchell, MP, considered that the BMA report undermined the Misuse of Drugs Act 1971.

I'm open minded about the question of legalization...But I am concerned about the therapeutic case because in 1971 cannabis, which had been available on prescription, after that time was transferred to Schedule I of the Misuse of Drugs Act, defined as a drug which has no therapeutic value. And since then everything has been changed by this BMA report which actually says that cannabis has therapeutic value.³⁸

Mitchell emphasized that a policy that led to the prosecution of patients brought the law into disrepute.

The law's coming into disrepute, prosecutions are being abandoned, we know that the courts are imposing very lenient sentences but people still get a criminal record... it is absolutely wrong that MS victims should be treated in that kind of fashion and driven to illegality. Something has to be done and quickly.³⁹

Mitchell, prior to the conference had taken a delegation with the Alliance of Cannabis Therapeutics to the Department of Health but found he could make little progress.

It's a chicken and egg situation in which the Home Office says it won't do anything because there is no research, but no research is done because it's illegal, and meanwhile thousands and thousands of multiple sclerosis sufferers are being forced into the backstreets into the illegal market to buy something that they know is helpful in the treatment of their condition.⁴⁰

The conference raised the public profile of cannabis therapeutics and the controversy of the legal situation. The BMA report gave campaigners ammunition against government policy and the confidence to move the process of medicalization forwards. The press picked up on splits in government over best approach to cannabis.

The Home Office Minister told Mr Flynn in the Commons there was no medical evidence that cannabis provided medicinal benefits. The Home Secretary Jack Straw has maintained a tough line in resisting all pressure for cannabis to be legalized... ..but highlighted the change in attitude from Frank Dobson, the Secretary of State for Health, who indicated that if medical evidence could be found, he would have no objections to cannabis being legalized for medicinal use. Mr Flynn intends to challenge the Home Office again with the BMA findings.⁴¹

The report was used by both campaigners for change and those in favour of the status quo. The conclusion, for example, whilst it recognized the potential therapeutic value of cannabinoids, steered clear of herbal cannabis itself and recommended further research prior to access being granted.⁴²

But the significance of the report was that a respected medical institution had recognized the potential of cannabis therapeutics. It legitimized research into cannabinoids if not cannabis and provided substantial pressure for a change in legislation for medical purposes. The House of Lords report which followed closely the publication of the BMA report was able to build on the BMA's acknowledgement of potential therapeutic uses of cannabinoids and provided pressure for action.

The Role of the Select Committee. The House of Lords Science and Technology Committee. Cannabis: The Scientific and Medical Evidence, 1998

The House of Lords Science and Technology Committee report on the therapeutic use of cannabis marked a milestone when it was published in 1998. Where the BMA had accepted therapeutic use, the Science and Technology Committee made extensive recommendations to about what to do with that advice. Select committees operated in both the House of Commons and the House of Lords and monitored the work of government departments. The Science and Technology Committee established in 1979 was one of the main investigative committees in the House of Lords with inquiries undertaken by two sub-committees. For each inquiry members were drawn from the main committee and additional members chosen for their relevant expertise. At the end of an inquiry a report, including evidence, findings and recommendations were presented to the main Committee and reports were published and debated in the House of Lords. The Committee worked independently of government and was free to choose its own topics. In February 1998, the House of Lords announced an investigation into the recreational and medical use of cannabis.⁴³ It was the first time cannabis had come under the spotlight of a select committee. The report explained the decision to investigate cannabis.

In the light of this heightened interest in cannabis, and particularly the report by the BMA, we decided to examine the scientific and medical evidence to determine whether there was a case for relaxing some of the current restrictions on the medical uses of cannabis.⁴⁴

The interest of individual Lords was important in the choice of cannabis. Les Iversen, a retired Professor of Pharmacology at Oxford University, and the special advisor to the cannabis committee explained,

That group is an interesting bunch of retired scientists, doctors, lawyers, all with some interest in science and technology... They choose a couple of topics they want to review entirely of their own initiative.... because the chairman of the sub-committee was a pharmacologist and had an interest in cannabis.⁴⁵

Lord Walton of Detchant, a former neurologist who had previously worked with MS patients explained the focus, *'the Select Committee became aware that a number of well-meaning people with MS were being prosecuted.'*⁴⁶ The committee approached the problem from the patient perspective rather than from concerns generated by the misuse of drugs which had been the focus of earlier expert discussion.

A sub-committee was established with Lords drawn from a range of disciplines but particularly from chemistry, pharmacology and neurology, some of whom during their careers had witnessed the use of cannabis by patients to treat intractable diseases. The Chair, Lord Perry of Walton, was a retired Professor of Pharmacology from Edinburgh University who had been instrumental in the development of the Open University. Other members included Lord Porter, Noble Prize winner for Chemistry; Lord Walton of Detchant; Lord Porter of Luddenham, a chemist, Lord Butterfield, a medical researcher; Lord Rea; Lord Soulsby of Swaffham Priory, Emeritus Professor of Animal Pathology; Lord Butterworth, a lawyer and university administrator; Lord Carmichael of Kelvingrove; Lord Dixon-Smith, Lord Kirkwood, a judge; and Lord Nathan, a solicitor.

The terms of reference were wider than those of the BMA report, and so the Committee inquired into, *'the science behind the arguments over the use of cannabis and its derivatives for medical and recreational purposes.'*⁴⁷ It also incorporated discussion of recreational use *'we have also considered whether the continued prohibition of recreational use is justified on the basis of the scientific evidence of adverse effects,'* but it emphasized that it would not cover issues such as prevalence of cannabis use, behavioral or social aspects of drug taking, law enforcement, any relationship between drugs and crime, and the extent to which cannabis contributed a gateway to drug culture.⁴⁸

Iversen drafted questions for the committee and he was responsible for calling a wide range of witnesses.⁴⁹ Researchers, like Pertwee, provided the pharmacologist's viewpoint with evidence of laboratory research and potential clinical applications. Clinicians, such as William Notcutt, presented on clinical research, and all provided positive feedback about clinical research. Professional bodies, such as the Royal

Pharmaceutical Society, and BMA also contributed. Dr Geoffrey Guy provided the industry perspective and discussed his interest in setting up a small biotechnology company to investigate ‘whole plant’ cannabis. The patient perspective was included with patients and user activists, including Clare Hodges and representatives of the MS Society. Relevant government departments including the Home Office and the Department of Health provided additional witnesses. Funders such as the MRC were included, as were advisory groups, including the ACMD. The committee provided an important forum to bring disparate work and perspectives under one umbrella and its conclusions were based on a wide spectrum of stakeholders.

The report made seven recommendations to stimulate research and change policy. The first recommendation urged that clinical trials of cannabis for the treatment of MS and chronic pain be mounted as a matter of urgency. Support for clinical trials was not unanimous. Professor Griffith Edwards, who had previously sat on the ACMD committees of the 1970s, provided evidence as a witness for the ACMD along with two other psychiatrists, Malcolm Lader, and Morfydd Keen. Edwards had always been wary of medical cannabis and he queried the value and ethics of diverting scarce MRC funding to large-scale clinical trials and argued, *‘it would be reasonable to investigate the matter but I do not believe it would be reasonable to go through a controlled trial.’*⁵⁰ If the ACMD delegation was wary of starting trials, delegates were also concerned with the misuse of drugs should cannabis-based drugs be developed and licensed. Edwards feared the potential for the misuse of prescriptions. However, the demand for clinical trials was overwhelming from most witnesses. The Department of Health accepted the legitimacy of demands for therapeutic cannabis and appeared keen to encourage trials.

*We do see that societies such as the MS Society do have a genuine interest in the potential for therapeutic benefit...I hope I have made it clear that the Department of Health would wish to do all it could to support and facilitate that initiative.*⁵¹

The MRC was brought on board to solve funding issues and it appeared willing to speed up the process *‘if there was a need for clinical trials in this area, we would be prepared to consider them out of the usual round of consideration of clinical trials.’*⁵² The

feasibility of clinical trials was already being facilitated by the emergence of a Royal Pharmaceutical Society working party on clinical trials protocols, and the involvement of GW Pharmaceuticals. With these aspects in place the Committee was keen to see trials go ahead, as Lord Walton explained,

*We did say that cannabis derivatives should continue to be controlled drugs because we did not approve the so called recreational use of cannabis....but we were happy to approve properly designed studies of its medical use.*⁵³

One more contentious aspect was the form of cannabis to be studied and its delivery method. Conflict emerged between groups, such as the BMA, the Association of Chief Police Officers, and the Christian Institute, a charity which promoted the Christian religion in the UK, all of whom supported research into the constituents of cannabis, and those such as Guy and Professor Wall, who supported research into ‘whole cannabis’. The Minutes recorded,

*Professor Wall argues in favour of trials of cannabis rather than pure cannabinoids. He criticises the BMA report for recommending that trials be confined to synthetic cannabinoids; he considers that it would be premature...to assume that the only active substance in cannabis is THC.*⁵⁴

The Royal Pharmaceutical Society showed support for ‘whole’ cannabis and the MRC viewed the comparison as important, provided a standardized product was available. GW Pharmaceuticals made this a possibility as the company indicated its willingness and ability to produce a standardized mixture.⁵⁵ The Lords, guided by Iversen’s questions, pushed the issue of research into herbal cannabis, and pressed the issue when questioning witnesses. In particular, they appeared to accept the arguments of patient activists who complained about the synthetics in contrast to herbal cannabis. Subsequent clinical trials tested both synthetic THC and extracts of cannabis. GW Pharmaceuticals, the one UK company with a licence to produce cannabis-based medicines, was designed around the production of extracts of cannabis.

The second recommendation related to the mode of administration of cannabis,

*Research should be promoted into alternative modes of administration... which would retain the benefits of rapid absorption offered by smoking, without the adverse effects.*⁵⁶

Modes of administration of cannabis had long been a controversial subject. The BMA had clearly been against the use of smoked cannabis. The select committee, however, did not rule out initial experiments with smoked cannabis, but did not contemplate an eventual therapeutic based on this method and therefore placed pressure on the development of alternative modes of administration. Lord Walton explained ‘*We could not condone smoking cannabis as we were carrying out a major campaign to ban smoking in public spaces, and there was good evidence that smoking cannabis was just as potentially carcinogenic as smoking tobacco*’.⁵⁷ But smoking was seen as a preferred method by patients and the need for a compromise stimulated research into other forms of administration, and preferably one that would divide medical from recreational use. GW Pharmaceuticals appeared to offer a solution to this problem through the development of a novel delivery system, the sublingual spray.⁵⁸

The impact of policy on research was examined by the committee and its recommendation on this aspect may have contributed in part to a shift in the policy environment on cannabis in subsequent years. Whilst the committee maintained that cannabis and cannabis derivatives should remain controlled drugs it argued for amendments to legislation. A pragmatic approach was required to deal with patient pressure. The Alliance for Cannabis Therapeutics was particularly keen to see changes that would immediately impact on patients to mitigate the long drawn out process of research and regulation before any new drug would reach patients. Researchers also indicated that the legal situation hindered research. The committee took these concerns on board in making its third recommendation which was the most controversial in that it required the downgrading of cannabis under the Misuse of Drugs Act a move which would have permitted the prescription of cannabis. The report suggested,

The Government should take steps to transfer cannabis and cannabis resin from Schedule 1 of the Misuse of Drugs Regulations to Schedule 2, so as to allow doctors to prescribe an appropriate preparation of cannabis, albeit as an unlicensed medicine and on the named-patient basis and to

*allow doctors and pharmacists to supply the drug prescribed. This would also, incidentally, allow research without a special license from the Home Office.*⁵⁹

Amendments to the law surrounding cannabis would have allowed prescription of cannabis-based drugs and would have had the additional advantage of creating a boundary between medical and recreational use. It was argued that such a move would support rather than weaken the drug control system.

*Legalising medical use on prescription, in the way that we recommend, would create a clear separation between medical and recreational use... We believe it would in fact make the line against recreational use easier to hold.*⁶⁰

If government was to contemplate a shift of cannabis from Schedule I it was required by law to consult the ACMD and therefore the fourth recommendation was to do just that. The fifth recommendation related to the international policy and recommended that the issue of scheduling of cannabinoids should be raised with the WHO. To counter fears over the potential diversion of prescription drugs and any link to recreational use the final recommendation was that if doctors were permitted to prescribe cannabis on an unlicensed basis, the medical professional bodies should provide firm guidance on how to do so responsibly and that the professional regulatory bodies should set in place safeguards to prevent diversion to improper purposes. This would bring the 'ownership' of cannabis to medical bodies.

The results of the select committee were made public and both the final report and the book of evidence were published. Government was expected to comment on Select Committee findings. The cannabis report created a stir when it was published on 11th of November 1998, heightened by the fact that the government rejected the report on the morning of its publication. The government admitted that it had departed from the usual convention in case its silence raised speculation that it regarded the questions around rescheduling open, thereby inviting hints of policy change.⁶¹

The government made the case that to protect patients it was not prepared to make changes prior to potential drugs passing through the existent regulatory process and that no interim measures would be introduced. Iversen described the response,

*The government on same day, before the ink was dry, said they were not going to make any changes to the law. In other words they dismissed it out of hand. But that was no knee jerk reaction, everyone expected that.*⁶²

The reaction was not unexpected. Previous reports that had called for re-classification had been rejected. The issue was debated in the House of Lords in December. Lord Perry criticized the government's reaction which appeared to be based on concerns already addressed by the Committee. Over the issue of efficacy and safety, Lord Perry argued that cannabis was already being used in the community and a more pragmatic response would be to regulate such use.

*The Government argues that prohibition protects patients... Significant numbers of sufferers are taking cannabis... in defiance of the law and without medical supervision or quality control; our recommendation would enable the health professions and the pharmaceutical industry to collaborate to provide appropriate preparations.*⁶³

The select committee questioned the nature of acceptable evidence and the interpretation of that evidence. In the committee's opinion enough evidence existed, even if it was largely anecdotal, and the committee added pressure to carry out clinical trials which remained the most accepted form of 'evidence.' Government concern, that a change in legislation, would reduce research was rejected as inaccurate and the opposite case was made that research was hindered by legislation.

*The Government argue that permitting prescription now would reduce the momentum of research. On the contrary, we found evidence... that research has been held back by the stigma and bureaucracy associated with the status of cannabis as an illegal drug.*⁶⁴

The grounds on which the government rejected the advice were brought into question. First, if patients were the priority on what basis should decisions be made - safety or quality of life? Lord Perry argued,

*Our report shows that if cannabis is used to treat patients on the prescription of a doctor, the risk to the patient is vanishingly small.. many patients would regard their safety as only their second priority after the quality of their lives. Should not the Government share that view?*⁶⁵

Second, the transparency of the rejection was questioned with concerns raised over whether decisions were based on the scientific evidence or social grounds. Lord Perry asked,

*Is their attitude coloured by social, economic and criminological considerations to which our inquiry was not addressed? Those considerations are only pertinent to the recreational use of cannabis.*⁶⁶

The government demonstrated that it remained resolutely against re-scheduling or prescription prior to trials as it believed that *'such a move would be premature.'*⁶⁷ In particular, the government argued that to allow prescription of herbal cannabis would restrict research and it was able to refer to the BMA's conclusions on this aspect. Nor was the government inclined to consult the ACMD as it feared this would encourage speculation that policy change was likely when it was not.

*It would have been disingenuous to seek a view having already decided that the recommendations would not be accepted.*⁶⁸

The government's apparently intractable position drew criticism from different quarters. Mike Pringle, Chair of the Council of the Royal College of General Practitioners, declared, *'I think the government is being unnecessarily cautious. The main interest here is the care of patients and the relief of patient suffering.'*⁶⁹ Conflict rose over the meaning of the term 'care of patients' as for some GPs it meant that when faced with patients with intractable disease, it was the ability to offer some treatment and relief, while for government the focus was on provision of 'safe' medicines.

The report attracted a degree of press attention. Iversen explained later the report, *'caused some interest in the conclusion that there were genuine medical uses, the dangers had been exaggerated and more research was needed.'*⁷⁰ It reinforced the public perception that there were medical uses for cannabis and that any dangers had

been exaggerated. The press picked up on the divisions between the BMA and House of Lords reports

The BMA says it is not 100% behind a report by the House of Lords Science and Technology Committee backing the use of cannabis for medicinal purposes. The BMA, which has previously supported more clinical trials into the medical use of cannabis, says legalising cannabis is not the answer. It believes only cannabinoids - part of the cannabis plant - should be used in medicine.⁷¹

But according to Iversen the report set the 'official seal of approval' for medical research into cannabis. Behind the scenes moves were taking place in regard to both therapeutic cannabis and cannabis within drug policy. Lord Walton later argued that the government, in time, took note of most of the recommendations including rescheduling.

In general, the report was approved by government; they supported the need for further research and for reclassification of cannabis on which they consulted the ACMD.⁷²

Whilst the recommendation to reschedule cannabis was rejected the government left an opening for the process of re-medicalization. It gave assurances that if quality, safety and efficacy could be demonstrated, then cannabis would be permitted as a prescription medicine. In making the lack of clinical trial data the restraining factor it had to facilitate clinical trials. It agreed to license trials that involved cannabis as well as cannabinoids and the Home Office Drugs Inspectorate was described as willing to discuss research-related licensing issues. The frail evidence-base gave the government the opportunity to defer the issue but it also meant that clinical trials of both synthetic and herbal cannabis proceeded. Those involved in the Select Committee claimed some responsibility for the advancement of re-medicalization.

Those involved in House of Lords would like to think it was some sort of response to the fact the House of Lords said there should be more research more proper trials.....It was a sop towards saying we were doing something towards this.⁷³

Even if it was merely a sop, it still forwarded the process of re-medicalization. Iversen commented, 'The report made some impact on future moves and helped stimulate the

*idea that there should be a proper controlled trial which the MRC took up and sponsored.*⁷⁴ Importantly the House of Lords helped smooth the path for industry involvement that took place after 1997.⁷⁵

The report contributed to a shift in the policy environment around cannabis generally. Certainly some of those involved in the Committee considered it had served a useful purpose. Lord Walton commented, *‘partly as a result of our report, though I can’t guarantee that, the Government downgraded cannabis.*⁷⁶ Iversen pointed out that the report came at an opportune time,

*It happened to be at a time when the Government was beginning to think about relaxing the laws on cannabis. Blunkett, the Home Secretary in 2001 suggested to the Home Office they consider the evidence for downgrading of cannabis.*⁷⁷

Stakeholders had come together at a time when there was more flexibility in attitudes towards the control of cannabis and internationally moves were afoot to open the door to cannabis-based medicines.

The UK and international policy

Government may also have been influenced by the changing attitudes of the international drug control agencies. The INCB had been hostile to cannabis since its inception under the 1961 UN Single Convention.⁷⁸ Presidents had taken a particular interest in the mental health aspect. Hamid Ghodse, Professor of Psychiatry and International Drug Policy at the University of London had been a Director of the International Centre for Drug Policy at St George’s, University of London, a member of the INCB since 1992 and had held the Presidency in 1993, 1994, 1997, 1998 and 2001. He became interested in cannabis from the mental health perspective in the 1980s which he continued through his role in the international arena.⁷⁹ Despite concerns the INCB could not ignore the development in the medical sphere, nor the pressure for compassionate access to cannabis. The 1998 annual report admitted that *‘the Board is aware that there is a need to investigate... medical use and...there is a growing interest among the medical community, public and media.*⁸⁰

Its changing attitudes to therapeutics may be because it viewed flexibility as a means to maintain the integrity of international drug policy. By 1998, Ghodse, by then President, encouraged the INCB to push for governments to carry out research into therapeutics in order prevent medical cannabis being hijacked by the legalization campaigns.⁸¹ Ghodse later explained the incentive,

*... to separate the political and medical aspects...and to encourage governments to do serious, scientific research on the alleged medical usefulness of cannabis so that if its effectiveness is established, it will be a drug no different from most narcotic drugs and psychotropic substances. It can then go through the process of re-scheduling as with any other controlled medicine. If it is shown not to be effective it will not provide ammunition to those using medicine for different objectives.*⁸²

However concern remained over the relationship between cannabis medicine and recreational use.

*The Board has noted with regret how possible medical usages of cannabis have been used to justify the legalization of call cannabis use. The Board welcomes and encourages serious scientific research on the alleged medical properties of cannabis...but warns against misusing these research efforts for “blanket” legalization purposes.*⁸³

The treatment of cannabis appeared to have the power to disrupt the entire drug classification framework. In contrast to comparisons that were emerging of cannabis with socially acceptable licit drugs such as alcohol and tobacco, the INCB found it important to maintain cannabis' close ties to controlled, narcotic drugs.

*Should the medical usefulness of cannabis be established it will be a drug no different to most narcotic drugs and psychotropic substances. This means that cannabis used for medical purpose would be subject to licensing and other control measures forseen under the international drug control treaties.*⁸⁴

Ghodse' view was that the INCB stance gave the green light for research and stimulated research in the UK, such as the MRC clinical trials.⁸⁵ Researchers in the UK denied that the INCB stance or indeed that of any of the international agencies had much impact.⁸⁶

Was it rather that the INCB wanted to catch up with events that had moved beyond its ability to control? But in the UK the government tone, if not policy, was changing. In the UK, clinical trials and industry involvement went forward after the House of Lords report and the following years saw the establishment of the clinical trials and the attempts at licensing cannabis-based drugs and in the process contributed to wider drug policy debates. But whilst the process of re-medicalization was to move forward potential changes to the classification system proved more problematic.

Rescheduling cannabis: Drugs and the law, Report of the Independent Inquiry into the Misuse of Drugs Act 1971

The issue of medical cannabis became more politicized and integrated with calls for re-scheduling in expert reports after 2000. One of the landmark reports that focused on the rescheduling debate was the *Drugs and the Law, Report of the Independent Inquiry into the Misuse of Drugs Act 1971*, otherwise known as the Runciman Report, released in 1999.⁸⁷ This aimed to tackle issues that the House of Lords had not covered. Established in August 1997 by the Police Foundation with the assistance of the Prince's Trust, it was chaired by Viscountess Runciman, a long standing member of the Advisory Council on the Misuse of Drugs, Chair of the Council's Criminal Justice Working Group and Chair of the Mental Health Act Commission. Members included representatives from: drug service organizations, such as Alison Chesney, Chief Executive of the Cranston Drug Services; the legal profession including, Rudi Forston, Barrister at Law, Middle Temple and founding member of Release; the police service including, John Hamilton, the Chief Constable of Fife Constabulary and academics including Professor David Nutt, Head of the Mental Health and Psychopharmacology Unit at the University of Bristol; Simon Jenkins, the former Editor of *The Times*; Ian Wardle, Chief Executive of Lifeline Project Limited, and Annette Zera, Principal of Tower Hamlets College, London.

The Committee reviewed the 1971 Misuse of Drugs Act. It argued that the classification system needed to be more closely related to scientific evidence of relative harm. Cannabis was the focus of one chapter in which it was considered in relation to

the harms of other illicit drugs and it was concluded that cannabis was less harmful than the other illicit drugs and that therefore the current law was problematic.

If our drugs legislation is to be credible, effective and able to support a realistic programme of prevention and education, it has to strike the right balance between cannabis and other drugs.⁸⁸

The Committee concluded that there was little evidence that the law was effective as a deterrent. It, like the ACMD before it, urged reclassification of cannabis to from Class B to Class C and from Schedule 1 to 2 of the Regulations of the Misuse of Drugs Act, a move which would have allowed supply and possession for medical purposes. Within the discussion of cannabis, therapeutic use played an important part in relation to its impact on the Misuse of Drugs Act.

We conclude that there is evidence that there are therapeutic benefits from the use of cannabis by people with certain serious illnesses and that these benefits outweigh any potential harm to themselves. We therefore agree with the House of Lords Select Committee that cannabis and cannabis resin, together with tincture and extracts not covered by the 1971 Convention, should be transferred from Schedule 1 to Schedule 2 to the 1985 regulations. That would automatically ensure that doctors who prescribed such substances were not criminally liable. The same would apply to their patients in possession and doctors or pharmacists who supplied cannabis.⁸⁹

The Committee had little to add to the conclusions of the BMA and House of Lords report other than, on the whole, to endorse and further their recommendations.

We appreciate the doubts of the British Medical Association over how to control and assess dosages of raw cannabis. But these seem to us insufficient reasons for preventing prescription where doctors, at their own risk on a named-patient basis, believe that their patients will benefit.⁹⁰

In the light of the medical conditions for which medical cannabis was being investigated attitudes to the form and delivery methods of cannabis were also undergoing change.

While understanding the reservations expressed by the British Medical Association and the House of Lords Select Committee about administration by smoking, this seems to us a very minor matter given the seriousness

of the conditions for which prescription of cannabis seems likely to be beneficial.⁹¹

The report called for immediate changes prior to results of clinical trials. It rejected one government fear: that of the misuse of prescriptions, and noted that the ability to prescribe heroin for pain relief had not caused a problem.

We do not share the Government's anxiety about the capacity of GPs to withstand pressure for the prescription of cannabis. There is no evidence that this has been a problem where the prescription of heroin for pain control is concerned.⁹²

The Runciman Committee built upon the House of Lords demands for compassionate access to medical cannabis and called for a legal defence based on medical grounds.

As the Government has rejected the House of Lords recommendations and it will be some years before a standard licensed cannabis product is available, we recommend that there should be a new defence of duress of circumstances on medical grounds for those accused of possessing, cultivating or supplying cannabis... This approach would comply with our international obligations under the United Nations conventions and enable spurious defences to be rejected.⁹³

The Committee reported in March of 2000 and the Home Secretary, Jack Straw, rejected reclassification. But he promised that the remaining recommendations would receive serious consideration. Meanwhile the report received considerable media attention and was generally well received. *The Independent* newspaper not surprisingly given its previous line on cannabis, reported the dismissive government response as did the BBC.⁹⁴ The House of Commons Home Affairs Select Committee pressured for a full response from the Home Secretary, but when government responded in full in February 2001 it rejected most of the key recommendations. Viscountess Runciman expressed her confidence in the enduring quality of the report,

Our recommendations on cannabis were by far the most far-reaching and they were meant to be, because we think that that is where the law is, in a sense, most defective.... this is a good report, has staying power and that its time will come.⁹⁵

She appeared confident the recommendations would stand the test of time and policy change would be implemented at an opportune moment. When the report was discussed by the Home Affairs Select Committee in June 2000 it came in for criticism over its independence and for its “soft” view on drugs.⁹⁶ Runciman was scathing about the government’s response and claimed, *‘it also leaves us with a law that in relation to cannabis produces more harm than it prevents.’*⁹⁷

Pressure continued to build for a rethink of drug policy and drug regulation. Therapeutic aspects of cannabis had again been headlined with the release in March 2001 of the second House of Lords inquiry into therapeutic cannabis, a follow-up report to their 1998 report.⁹⁸ This inquiry covered new research that had taken place since the initial report but also dealt with the legal situation and growing concerns over the prosecution of those using cannabis medically. The terms of reference were,

*To examine the current state of research into the therapeutic uses of cannabis, the roles of the Home Office and the Medicines Control Agency in the licensing of cannabis-based medicines, and more recent issues relating to the prosecution of therapeutic cannabis users.*⁹⁹

The 2001 report reiterated the points of the 1998 report but with clinical trials underway for the first time the role of regulatory and licensing bodies came under scrutiny. Once again reconsideration of regulatory requirements was urged. At that point there was more receptiveness to the concept. The report referred to an apparent change in attitude by the government to prescription of cannabis-based medicines.

*We are pleased to note that the Government now displays a more encouraging attitude towards the licensing of therapeutic preparations of cannabis...In effect, the Minister assured us that once a safe, effective, cannabis-based medicine had been licensed by the Medicines Control Agency, the Government would actively co-operate in permitting it to be prescribed.*¹⁰⁰

The long timescale for the licensing of cannabis-based medicines was deemed to relate to the fear that medical use might stimulate greater recreational use rather than objections to medical cannabis itself.

*Up until now we have sensed that the authorities have been dragging their feet, at least partly because they may have feared that permitting therapeutic preparations of cannabis to be prescribed would be interpreted by the public as a move towards allowing recreational use.*¹⁰¹

But by 2001 government viewed the re-medicalization of cannabis as a means to provide a clear distinction between medical use and non-medical use. The development of clear medical and non medical structures for cannabis would weaken calls for decriminalization and make it easier for Government to clampdown on recreational use if desired.

*There is now a much sharper awareness of the distinction between medicinal use of cannabis and recreational use of cannabis in the public debate... We are pleased, too, that the Minister now shares our view that, were the law relaxed on the therapeutic use of cannabis, the Government's hand in suppressing illegal, recreational use would be strengthened.*¹⁰²

But the House of Lords had key concerns over this stage of the process of re-medicalization. The progress in clinical trials was slow and it appeared that the need for licences and a continued stigma around cannabis still inhibited research. In the meantime, it was viewed as undesirable to prosecute therapeutic users. In addition there were fears that the MCA had failed to take a balanced, objective view of cannabis-based drugs and that it needed to reconsider its position on cannabis-based drugs that had attempted to pass through the regulatory system. The report captured the attention of the press with headlines such as '*Lords back cannabis use.*'¹⁰³

The General Election in June 2001 saw the re-election of the Labour government. The new government seemed more inclined to reconsider cannabis and in July 2001 the incoming Home Secretary David Blunkett, was reported as wanting to re-open the drug debate. Pressure mounted when the Home Affairs Select Committee in July 2001 announced its intention to hold an inquiry entitled, '*The Government's Drugs Policy: Is it working?*' Later that year came an indication that policy change might be underway. At a Home Affairs Select Committee meeting the Home Secretary David Blunkett announced that he favoured the reclassification of cannabis and asked the ACMD to

review the classification in the light of the scientific evidence. At the meeting he made it clear that subject to the satisfactory outcome of the clinical trials, he would approve a change to the Misuse of Drugs legislation to enable the prescription of a cannabis-based medicine.

*Should this programme be proved to be successful, I will recommend to the Medicines Control Agency that they should go ahead with authorising the medical use of this for medical purposes. In the event of the successful completion of clinical trials and a positive evaluation by the MCA, we recommend that the law is changed to permit the use of cannabis-based medicines.*¹⁰⁴

The Home Affairs Select Committee signaled its agreement that the dangers of cannabis relative to other drugs had been overstated and the greater public health danger might lie in the loss of creditability of the entire drug control system.

*Whether or not cannabis is a gateway drug, we do not believe there is anything to be gained by exaggerating its harmfulness. On the contrary, exaggeration undermines the credibility of messages that we wish to send regarding more harmful drugs. We support, therefore, the Home Secretary's proposal to reclassify cannabis from Class B to Class C.*¹⁰⁵

Whilst these moves to reclassify cannabis took place therapeutic issues were brought back to the table with the government response to each of the House of Lords reports recommendations released in December of 2001. The government reiterated its encouragement of clinical trials, 'The Government has consistently made it clear that it welcomes clinical trials into the therapeutic use of cannabis... this remains the position.'¹⁰⁶ The government appeared to take a relaxed attitude to the criminal justice system taking on a sympathetic view of medical users of cannabis.

*While the law can make no distinction on the criminality of the possession of cannabis for recreational or therapeutic reasons, while the efficacy and safety of the latter remain unproved, the Government believes that the criminal justice system does allow for a sympathetic approach to the genuine therapeutic user.*¹⁰⁷

The government defended the MCA and the regulatory process.

The Government accepts that it should be impartial in its approach to licensing cannabis-based medicines..Development of cannabis-based medicines poses a number of very difficult scientific and regulatory problems. The MCA is treating these products in the same way as any other drug, taking account of all the information available on the balance of risks and benefits including relevant human exposure, in making their decisions. Whilst acting within the appropriate constraints of regulations that protect clinical trials subjects, the MCA is working closely with those developing these products to identify solutions to the specific problems. In doing so the MCA has contributed significantly to the progress of the development of these medicines.¹⁰⁸

The ACMD presented its report to the Home Secretary in March 2002, recommending that all cannabis products be reclassified as Class C and moved from Schedule 1 to Schedule 2 of Regulations of the Misuse of Drugs Act 1985, on the grounds that cannabis was less harmful than other substances within Class B. The report made reference to a possible link between chronic use of cannabis and mental illness, but stated that ‘no clear causal link has been demonstrated’. The impact on therapeutic cannabis was to split it from the drugs debate and to indicate that it could be treated as a separate issue.

The Council is aware, however, that clinical trials of cannabis derivatives are in progress. If, at some future date, one or more cannabis preparations become available as medicinal substances then the Council would advise about which Schedule, under the Misuse of Drugs Regulations 2001, they should be categorized. This matter, however, is entirely separate from the classification of cannabis under the Misuse of Drugs Act 1971.¹⁰⁹

In October 2003 MPs voted to downgrade cannabis and its derivatives to Class C, though cannabis possession remained an arrestable offence as the power of arrest was extended to Class C drugs. Reasons given for this alteration included a more accurate assessment of the harm caused by cannabis relative to other drugs, the continued need to control cannabis use and as a signal that the government desired to focus on the misuse of the most harmful Class A drugs, such as heroin and cocaine. It marked a change in the allocation of scarce resources from the control of ‘soft’ to ‘hard’ drugs. Debates in

the House of Lords featured consideration of the relative harms of cannabis compared with licit drugs, Lord Rea stating,

*Although cannabis can precipitate some mental illness it causes nothing like as much harm as alcohol or tobacco. Alcohol can kill people acutely-if they drink a whole bottle of spirits-quite apart from causing lingering death and we all know what tobacco can do in the long term. Those two substances are not class A, Class B, or Class C- they are not classified at all.*¹¹⁰

The amendments to the Misuse of Drugs Act 1971 came into effect in 2004 and the move attracted the ire of the INCB which reiterated it was against any moves which might weaken the international drug control framework.

*No government should take unilateral measures without considering the impact of its actions and ultimately the consequences for an entire system that took governments almost a century to establish.*¹¹¹

Whilst the INCB admitted that downgrading did not contravene any convention, it went so far as to express its fear that the move might send the wrong message and described the decision as a ploy to grab headlines. The INCB's fear was that that individual countries might bypass rather than seek to change the international drug control mechanism.¹¹² International moves to re-medicalize cannabis in particular came in for criticism.

*The Board has repeatedly expressed its concern that, without having reported conclusive research results to the WHO the Government of Canada and the Netherlands authorized the use of cannabis for medical purposes. The Board is also concerned that cannabis is used for medical purposes in some jurisdictions in the US without having definitive proof of its efficacy.*¹¹³

It therefore welcomed the US Supreme Court's decision to 'reaffirm that the cultivation and use even if it's for medical use should be prohibited'¹¹⁴ This ruling was intended to curtail individual states such as California which were taking a more liberal attitude to cannabis production.¹¹⁵ A backlash developed and criticism of the international drug control agencies and the 'war on drugs' intensified. When Canada permitted access to medicinal herbal cannabis it faced strong criticism from the INCB. Fazey argued that

the INCB criticisms of individual countries, in particular of Canada's policy, exceeded its role and that such criticism went, '*far beyond their remit*.'¹¹⁶ Iverson contrasted the conservative nature of the UN narcotic agencies towards cannabis with the WHO's changing approach, and the impression that the agencies had lost respect in the western world.¹¹⁷ The problems inherent in the drug control agencies, like the Commission on Narcotic Drugs and the INCB, and the failure to respond to changing circumstances in the face of limited success in drug control, raised questions over their decision-making process. But whatever the criticism of the INCB, and their criticism of challenges to the international drug control framework, in order to justify control they had signaled the go ahead to medical research. The need to separate recreational and medical use in order to maintain the Conventions encouraged research and funding into what otherwise might have remained an obsolete field.

Conclusion

A major alteration in attitudes took place towards cannabis in the period 1997-2004. Research and anecdotal reports filtered through to expert committees and professional organisations which released positive reports and the concept of cannabis as a medicine, rapidly replaced cannabis as a menace. As pressure mounted national and international agencies eased restraints on medical research in order to divide medical use from recreational use and funding and incentives again flowed into the field. Concerns shifted to focus on the form of cannabis utilised and its delivery methods. But the debates also opened up questions about the role and functions of the international control agencies and policies. The following decade would see the re-medicalization of cannabis hinge on success in clinical trials and regulatory systems and continued and intensified questions over systems of drug control.

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Chapter Eight

From anecdotal to evidence-based medicine. The role of clinical trials in the process of the re-medicalization of cannabis, 1980-2006

Clinical trials have been integral to the process of re-medicalization of cannabis. Randomised controlled trials (RCTs) had become the benchmark in biomedicine, and cannabis had to successfully perform in trials in order to become a licenced medicine again. In the US clinical trials of THC tablets in the 1970s moved cannabis away from anecdotal medicine towards evidence-based medicine. In the 1980s, these trials led to the licensing of Marinol (dronabinol) and Cesamet (nabilone) as anti-emetics or appetite stimulants. These drugs had limited uptake and were largely superseded for these uses but the process set a precedent. There remained much scepticism, and up until 2000, reports on cannabis' medical use remained largely anecdotal or dependent upon single case reports or at best small-scale clinical trials. Work that had been carried out was primarily focused on synthetic THC, rather than herbal cannabis. This chapter charts the growing interest in clinical trials on cannabis in the UK from different stakeholders which converged in the 1990s in a desire to see the production of additional cannabis-based drugs. Government was keen to see a distinct line drawn between illicit and licit cannabis use; MS patients were vociferous in their demands for access to a cannabis-based medicine or herbal cannabis; a number of clinicians who worked on pain and MS developed an interest in the potential of cannabis; and professional organisations such as the BMA, and the Royal Pharmaceutical Society pressed for clinical trials and attempted to draw stakeholders together. Two avenues opened up for clinical trials: one, an academic route with 'proof of principle' trials and another by GW Pharmaceuticals which aimed to license an extract of cannabis.¹ These developments led to large-scale, randomised double-blind controlled trials. They had mixed outcomes and demonstrated the problems of working on cannabis, on health problems that were difficult to measure such as pain, as well as issues specific to clinical trials: recruitment, retention and

outcome measures. At the time of writing trials had yet to lead to a cannabis-based drug licensed in the UK yet they were important in the process of re-medicalization.²

Cannabis and the importance of clinical trial methodology

Discussion of the production and licensing of any new therapeutic drug in the later part of the twentieth century cannot be discussed without reference to the development of evidence-based medicine and the rise of the randomised controlled trial (RCT).³ Clinical trials are broken down into four phases. Phase I establishes how a medicine works and dosage, and is based on healthy volunteers; Phase II tests safety and efficacy on small groups of patients with the relevant illness; Phase III tests both safety and efficacy in large groups of patients; and Phase IV is a post-licensing phase. If the drug successfully passes through the first three phases, it will normally be approved by a national regulatory authority, in the UK the Medicines and Healthcare products Regulatory Agency (MHRA, the Medicines Control Agency (MCA) prior to 2003) which is charged with ensuring that medicines and medical products work and are acceptably safe. If medicines are shown to be safe, and effective the MHRA will license a drug and provide a marketing authorisation (previously a product licence). In making regulatory and licensing decisions advice is sought from an advisory committee the Commission on Human Medicines (CHM), (the Medicines Commission and the Committee on the Safety of Medicines prior to 2005).⁴ There is an international element to trials, as in the 1980s, harmonization of clinical trial protocols was shown to be feasible across countries of the European Union. Coordination between Europe, Japan and the United States led to a joint regulatory-industry initiative on international harmonization known as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

For cannabis to become a legitimate therapy again it had to pass the benchmark: double-blind randomised controlled trial. Above and beyond the difficulties of researching a controlled substance, the RCT presented a specific set of issues for cannabis. Healy has shown the importance of the development of RCTs in the history of the development of psychopharmacology and demonstrated that not all drugs were

easily amenable to that form of evidence-based medicine, *'The match between drug therapies and RCTs is based on the idea that a drug embodied one active principle which had been isolated and could be delivered systematically.'*⁵ In attempting to explain some of the problems RCTs posed for the development of antipsychotic drugs, he illustrated how not all drugs could be considered within the framework of "magic bullets" but instead were complex cocktails of compounds containing a number of therapeutic principles.⁶ These issues were particularly pertinent to the progress of cannabis through the licensing system. As a highly complex plant substance, it was difficult for researchers to ascertain the form of cannabis to research and develop. Up to the 1990s, the only area that had been seriously investigated was THC as an anti-emetic which led to the licensing of nabilone and dronabinol. These drugs, which it was hoped would provide a licit version of cannabis, failed to fulfill this expectation as the drugs were heavily restricted and patients appeared to prefer herbal cannabis. In this context, the door opened for further investigations and in particular a need to research something more akin to cannabis itself and for additional applications.

The initiation and development of the UK clinical trials on cannabis. 1995-2000

Research began to support anecdotal evidence of cannabis' therapeutic role especially with the discovery of the endocannabinoid receptor system. Interest shifted out of the laboratory and into the clinic and gave a new legitimacy to cannabis. Cannabis had anecdotal evidence of benefit in the treatment of MS and pain, and by the mid-1990s that was where interest focused. MS had few treatments and the area of pain had not seen the introduction of a new drug for twenty years. In MS, only six trials with a total of forty one patients had been carried out, insufficient to consider licensing cannabis based medicines.

Individual clinician interest was a key factor in the focus of trials. Those clinicians who led the trials had an early interest in MS and, or pain and many had witnessed how the use of smoked herbal cannabis had been used by patients to alleviate their symptoms. Professor John Zajicek who led a MRC funded trial on MS, was a neurologist who had gained a PhD studying the cell biology of MS and he had wanted to move into the clinical aspects of MS. In 1995, he had moved to Plymouth where he

became involved in the clinical aspects of MS. Another clinician who began trials on MS and pain was Dr William Notcutt. Notcutt had qualified in Birmingham in 1970 and he had come across cannabis being used as a bush tea for alcoholism and glaucoma whilst he worked at the University of the West Indies in Kingston, Jamaica. In 1982, he moved to the James Paget Hospital at Great Yarmouth as a consultant anaesthetist, where he focused on chronic pain. He set up a Palliative Care Service in 1985 and introduced Patient Controlled Analgesia (PCA) for patients with post-operative pain. In looking at the history of pain treatment, he had come across references to cannabis and had observed patients self-medicating with the drug. In 1994, he accompanied patients and Professor Patrick Wall, an eminent pain specialist, to Parliament to campaign for access for patients to medical cannabis. Notcutt had begun testing nabilone on patients suffering from pain and MS when nabilone became available on a named-patient basis.⁷ Dr Anita Holdcroft was another clinician who had also come across the use of cannabis by patients and she had investigated its usefulness prior to the development of the major clinical trials. Her focus however was on acute pain rather than MS. She was anaesthetist who had worked in West Africa in the 1980s and when she returned to the UK in the early 1990s, she retrained in pain medicine and set up a pain clinic at the Hammersmith Hospital. It was an era when the basic science of pain medicine was emerging and her interest in cannabinoids was triggered when she found herself dealing with ‘*very limited management strategies*’⁸ for problems that were inadequately described or that had inadequate treatments. Whilst she had read of advances in pain management she found that they were not put into practice in the clinical environment.

This led to the development of small-scale trials.⁹ Holdcroft had one patient who suffered from familial Mediterranean fever, an inflammatory condition of the gut, and who used cannabis to reduce his symptoms. On discussion with the patient it was decided to develop a clinical trial.¹⁰ The trial took a year to initiate. The patient had been prescribed oral morphine, but self-treated with herbal cannabis. Dr Holdcroft struggled to obtain cannabis for the trial. Marinol was considered difficult to import, and Holdcroft was aware that the patient preferred herbal cannabis to THC. Fred Evans, Professor of Pharmacognosy at the School of Pharmacy, worked on inflammation, and he was able to provide small amounts of cannabis as a capsule. The MS Society, wary

of the drug's illegal status, refused to fund the study. In contrast, the Home Office appeared keen on the trial and wanted it scaled-up. This proved not to be feasible as finding other suitable patients was problematic.

The trial revealed issues that proved to be a problem with later clinical trials. Holdcroft's patient could obtain cannabis off the street and he knew that it helped with his pain. On the placebo he became irritable and he had to be persuaded to remain in the trial. This issue of retention would reoccur with a vengeance in later trials. But despite these problems the results of the trial were positive. The drug showed anti-inflammatory properties and highlighted significant reductions in additional analgesic requirements.¹¹ Holdcroft was able to show that cannabis use reduced the amount of morphine required to control pain. But this was only a very small scale trial (n=1): the study of one patient was not proof on its own. Others have argued that n=1 trials such as those used in psychological research might be a suitable alternative method, rather than favoured large-scale trials.¹² The trials of cannabis in small-scale studies meant experience was gained in the UK around the application of cannabis to MS and pain. Moffat recalled, that *'the clinical trials that had been carried out were either too small 20-30 patients or had no real objective end points.'* and pressure grew for large scale trials.¹³ The nebulous qualities of these health problems and complex therapeutic under investigation had both benefits and complications for the clinical trials and the licensing of resultant cannabis-based drugs.

Individual clinical research interests were brought together by professional bodies in the mid 1990s. By that stage professional bodies were prepared to become involved with cannabis and their influence and expertise facilitated the initiation of large-scale clinical trials. In 1995, the Council of the Royal Pharmaceutical Society, the regulatory and professional body for pharmacists in England, Scotland and Wales, took an active role in stimulating cannabis research. The Pharmaceutical Society issued a statement that noted that more clinical research was needed to investigate the potential therapeutic uses of cannabinoids in specific medical conditions. It suggested that since it would be some considerable time before the results of such research were available, there was a case for allowing doctors to prescribe cannabinoids for serious named disorders.

To this end the Pharmaceutical Sciences Group of the Royal Pharmaceutical Society, in conjunction with the MS Society and with the support of the BMA, arranged a public meeting, '*The Therapeutic Applications of Cannabinoids*', attended by over one hundred and thirty people, at the School of Pharmacy in March 1997. The goal was to survey the evidence for the medical use of cannabinoids, to review the history, chemistry and pharmacology of cannabinoids and to clarify the legal position on using cannabinoids therapeutically.¹⁴

The meeting highlighted the need and pressure for research into medical cannabis. Dr Anita Holdcroft recalled,

*Different vocal groups were there. They strongly advocated the medicinal use of cannabis. We could see that some patients were getting value out of it. There were concerns ... they had no idea of the doses. They were probably taking too much.*¹⁵

Medical use of herbal cannabis existed within the patient community, and it could be argued that one justification for trials was to ascertain an efficacious and safe dosage. The meeting was a catalyst to the development of clinical trials. Anthony Moffat of the Royal Pharmaceutical Society (RPS) and Professor at the School of Pharmacy described how discussions at the end of the meeting stimulated his interest to move the process forward,

*Anita Holdcroft and I, and the Dean of the School of Pharmacy were there together and she said 'Why doesn't somebody do some clinical trials' ...I thought well she's absolutely right.*¹⁶

But the question was whether trials were feasible in the political climate. It appeared there was support from enough quarters to allow trials to go ahead. Anthony Moffat and Vivienne Nathanson from the BMA, and the School of Pharmacy met with Kenneth Calman, Chief Medical Officer, who agreed it was a good time to do trials.¹⁷ Alan Macfarlane, Chief Inspector of the Home Office Drugs Branch indicated that a study would be viewed favourably but stressed the necessity for good quality proposals.

In order to develop such proposals informal networks of interested researchers such as the Clinical Cannabinoid Group convened by Dr Pertwee were put on a more formal footing and the Clinical Cannabinoid Working Group under the auspices of the Royal Pharmaceutical Society was established to bring all interested parties together to work out the means to carry out trials. The group comprised of influential stakeholders and was chaired by Professor Sir William Asscher, former Chairman of the Committee on Safety of Medicines. It included representation from the NHS Research and Development Directorate, the MRC, the MS Society and researchers including Professor Pertwee, Dr Zajicek, Dr Anita Holdcroft and Dr William Notcutt. Anthony Moffat, the RPS's chief scientist, explained the Society's involvement,

The Society has a long-standing involvement with research into the medicinal benefits of cannabis and the publication of this work shows that cannabis has some therapeutic effect in the treatment of MS. The Society's policy on cannabinoids (the active constituents of cannabis) was to see clinical trials undertaken to show the therapeutic benefits.¹⁸

The working group met in July and August 1998 and had a clear remit: To prove the value of cannabis, not to bring a drug to market. Sir William Asscher explained,

We were quite insistent we would have no involvement in the development of drugs, merely the proof of principle. The drug industry would have to take it up.¹⁹

The objectives of the working group were to produce guidelines by which future trials could take place with the aim of speeding up and facilitating the process of approving and funding trials, trial development and publication of results. The group met over the eighteen months to hammer out potential trial designs.²⁰ Clinical trial design and objectives were written into a document called a clinical trial protocol. The protocol operated as the 'operating manual' for the clinical trial, and ensured that researchers in different locations perform the trial in a similar way on patients with similar characteristics and was particularly important in multicentre trials.

Those eighteen months proved to be a significant period in the process of re-medicalization of cannabis, as other events were taking place which created a

changed environment around cannabis and which smoothed the path for clinical trials. In 1998, substantial pressure for clinical trials both by academia and industry emerged with the publication of the House of Lords Enquiry into the therapeutic use of cannabis.²¹ In its evidence to the House of Lords Report, which is examined in detail in chapter seven the Royal Pharmaceutical Society was unequivocal in its support for clinical trials. It recommended research should be encouraged into the mode of action of cannabis and the development of synthetic cannabinoids; and that the government should support clinical trials into therapeutic uses of cannabinoids for MS, nausea, pain, anorexia and epilepsy. In terms of the legal situation they stated that cannabinoids should be downgraded from Schedule 1 to Schedule 2 of the Misuse of Drugs Act 1985. Such a move would have placed them in the same context as opiates and bypassed the need for a Home Office licence for research. In relation to cannabis-based products that might emerge the Society recommended that they should be able to be prescribed by a GP.²² The House of Lords Committee took on board these recommendations and concluded,

*We therefore recommend that clinical trials of cannabis for the treatment of MS and on chronic pain should be mounted as a matter of urgency. We warmly welcome the fact that ...both Dr Geoffrey Guy and the Royal Pharmaceutical Society's working group under Sir William Asscher have set off down this route. We welcome the Asscher's group intention to compare the effects of a standardized preparation of natural cannabis with those of one synthetic cannabinoid already available, dronabinol.*²³

The House of Lords Report therefore stimulated both proof of principle trials, and also trials by industry which aimed to license cannabis-based drugs. Though the Report was rejected on the day of publication, attitudes in government towards the medical use of cannabis had shifted and it was indicated that the licensing process would be facilitated and few researchers found hindrances in this respect. Cannabis' illegal status provided political pressure and a flow of funding for research into cannabis, that many potential legal medicines did not attract. Zajicek commented on the background politics and the auspicious timing of the trials.

It was luck really. A time when there were a number of factors that all conspired together. There was a big push to make cannabis legal. The

*government wanted to test new treatments. New Labour didn't want to legalize. They wanted it to be tested. They were keen on getting results through scientific evidence.*²⁴

Patient experience and advocacy played an important role in the stimulation of trials. The patient perspective was particularly important in pain management. Holdcroft elaborated on the significance of pain and MS in the flexible attitudes in the UK towards cannabis.

*In pain you listen to what patient tells you...its very much a subjective assessment. So it seemed reasonable to follow up on their experience. It was also what MS people saying. Only really happened in this country..I think it was because there was some latitude in the use of cannabis (in the UK).*²⁵

User activism was important and Holdcroft recalled, ‘there was quite a lot of activity through the MS Society. They were starting really to lobby,’²⁶ The UK governments interpretation of the international conventions meant that it was possible for clinical trials to go ahead.

Funding clinical trials and the role of the MRC

The government was especially keen to support research that could provide a licit cannabis-based medicine and therefore eliminate the use of the medical argument for legalization of cannabis. But to do this it was necessary to have a better evidence-base, hence the need for trials. Zajicek argued that the illicit nature of cannabis and subsequent pressure from government helped direct funds into cannabis.

*We are lucky in that it's got a high profile in that it's a drug of abuse. If it wasn't I don't know if we would have funding now. I have a lot of colleagues that want to do clinical trials and can't. You need to have reasons to do onehaving politicians on your back is useful. It's good for us to some extent.*²⁷

Clinical trials have always been an expensive and complicated process. The support provided by the MRC was important both financially and to ease the burden of

multi-centre trials. Zajicek commented on the role of the MRC,

*We didn't have funding. So we approached the MRC. They were helpful in trying to make sure grant applications were successful And in facilitating the co-ordination of the study.*²⁸

The MRC was reorganized during this period and the cannabis trials benefited from the new structure. The MRC Clinical Trials Unit (CTU) was formed in October 1998 to continue with research programmes in HIV and cancer and with its activities in statistical methodology, meta-analysis and quality of life research. In addition, the CTU directed by Professor Janet Darbyshire aimed to initiate trials in new areas where there were important questions but where there was either insufficient infrastructure or few clinical trials. A MRC Trial Development Group advised applicants on cannabis trial designs to ensure that applications were highly competitive in obtaining funding. The MRC participated in the Royal Pharmaceutical Society's working party on therapeutic uses of cannabis. It reported to the House of Lords Committee that there was a shortage of high quality research proposals in the area and indicated that it would be supportive of funding clinical trials and would consider grant applications out of turn to speed up the process.

*It is particularly important that the potential for new medicinal drugs.... is not stifled by considering all cannabis-like compounds as medically unacceptable because of the abuse potential of the natural product. ... The MRC would be supportive of funding well-conceived clinical trials.... It is important to evaluate in a rigorous manner whether cannabis or cannabinoids do indeed offer any relief of symptoms in neurological disease.*²⁹

Holdcroft cited later the role of the House of Lords in encouraging the MRC to fund trials.

*The House of Lords put pressure on the MRC to do this study because they recommended trials. Normally trials are done by a pharmaceutical manufacturer rather than government and the MRC doesn't normally fund them unless for specific purposes.*³⁰

The result was that Zajicek's trial, CAMS, received an initial one and a half million pounds and Holdcroft's trial, CANPOP, half a million pounds from the MRC. Shortfalls were sought from specific disease charities such as the MS Society.

The development of clinical trials: Cannabis form, supply and administration.

A major question for the trials was the form of cannabis to study. Both the industry and proof of principle trials incorporated the study of extracts of cannabis as well as synthetic THC. GW Pharmaceuticals grew its own cannabis, and solved the problem of standardization and supply when it developed an oral-mucosal spray based on extracts of herbal cannabis. For the 'proof of principle' trials much debate took place over the forms of cannabis to trial. Zajicek explained,

We had to work out which drugs we were going to use. We knew that THC was likely to be the most active ingredient. THC was already being used because in US it had a licence in the form of Marinol for nausea related to cancer chemotherapy.... If THC worked we would be able to get it out quickly because it was already being manufactured and used. We wanted to put THC in there. But if it didn't work and there was something else in cannabis then we would be criticized so we had to include an arm with a cannabis extract.³¹

The trials were focused mainly on THC. Marinol was an obvious choice, and UNIMED was prepared to supply it free of charge.

But these trials marked a new avenue for clinical trials: extracts of cannabis. This was not without controversy as the use of an extract posed concerns. Some feared potential diversion of use, and others such as Professor Ashton and Professor Nathanson from the BMA were against the use of material other than a synthetic single entity chemical on the grounds that a botanical extract was a complex substance with unknown effects. Zajicek highlighted some of the difficulties involved in the investigation of a botanical extract.

It's very difficult to identify every last component. THC is manufactured so we know what is in there. In an extract from a plant there are tens of different cannabinoids and all other things such as flavinoids.³²

Nevertheless, pressure was mounting for evidence-based research into something more akin to the herbal cannabis with which patients self-medicated. GW Pharmaceuticals had decided to go down the extract route, and Professor Asscher's working group was keen to see this area investigated believing it was possible 'to overcome problems of standardization, and reap benefits of the whole plant.'³³ Professor Wall was also in favour of the investigation of an extract rather than pure cannabinoids and he criticized the BMA's position of testing only synthetic cannabinoids. Support for an extract was diverse: from the Royal Pharmaceutical Society, to researchers including Professor Roger Pertwee and patient groups like the ACT whose members were already using herbal cannabis and the MS Society which wanted to test all options. Holdcroft explained why those interested in pain wanted to pursue an extract.

We were starting to know what compounds were in the plant. There was a big lobby to use the plant rather than THC. For pain it was obvious you needed to use more than one drug... ..so the use of something that had a bit of something... no problem.... as long as we knew what was in it...³⁴

Technology had moved on and helped make clinical trials into extracts of cannabis feasible. The advent of mass spectrometry techniques in the 1980s made the original argument that it was not possible to define what was in a plant less powerful. Indeed instead of being viewed as problem, a mixture of substances was seen as potentially advantageous especially for pain and MS. On this basis, the protocols incorporated an arm that attempted to explore the effect of 'whole' cannabis.

The provision of an extract was more complicated than provision of THC. The School of Pharmacy had for the previous twenty years produced cannabis under the guidance of Fred Evans who had grown cannabis for the Home Office. Evans who was head of the Centre of Pharmacognosy, (1994-98) specialized in the irritant phorbol esters with pro-inflammatory and tumour promoting activities, biologically active principles of cannabis and herbal medicine. However, the School was not geared up to

provide the quantity needed for multi-centre clinical trials. Such large quantities were usually provided by industry. Furthermore, standardizing the product remained an issue. Initially, those who designed the protocols hoped that GW Pharmaceuticals might provide the extract arm but financial and practical constraints intervened. Zajicek had met Guy in the 1990s and had discussed a supply of material but GW, in its formative stages, did not have a product to commit and Guy would have required payment.³⁵ As in the 1970s, low or zero cost of research material was important. The presentation of the protocols at a Royal Pharmaceutical Society meeting in 1999 had presented the opportunity to introduce the project to potentially interested companies. A German charity, the European Centre for Immunological and Ontological Research produced Cannador, a standardized pharmaceutical preparation in the form of capsules which contained cannabis extract grown in Switzerland, and encapsulated in Germany. It agreed to provide the product free of charge. Ensuring continuous supplies of imported material however concerned researchers. Cannador depended on the ability of the charity to provide a continuous free supply, while Holdcroft raised the issue that the United States restricted THC production which might limit its usefulness for large-scale clinical trials.³⁶

Delivery systems related to the administration of herbal cannabis were a major stumbling block. The clinical trials of THC in the 1970s and 1980s were based on a capsule, but these had had problems in that those suffering from nausea found them difficult to take and the capsules had a long time-lag in comparison to smoked cannabis. Smoked cannabis however remained a pariah in an era of anti-smoking campaigns, though such trials were not totally ruled out. The House of Lords Report recommended, '*research be promoted into alternative modes of administration eg inhalation, sub-lingual and rectal*'.³⁷ The protocols however eliminated smoking as a delivery method. Zajicek explained the decision for the CAMS trial, '*It was decided at an early stage that the drugs would be administered in capsules by mouth because of the increased dangers of smoking such drugs*'.³⁸ The ultimate goal was a method of administration which provided the rapid absorption provided by smoking. GW Pharmaceuticals hoped to solve the administration issue by the production of a new delivery system for cannabis. But Zajicek had concerns about that, '*We knew from*

*conversations with other companies that this was going to be quite difficult because it's (a spray) quite an irritant.*³⁹ As a result the CAMS trial remained with the THC capsule route.

Ethical and bureaucratic issues had to overcome which were doubly difficult in the case of cannabis. In the UK a trial had to be approved by the Medicines Control Agency (MCA, which after 2003 became the Medicines and Healthcare products Agency, MHRA) and if approved a clinical trials certificate would be issued. Approval to study an illicit substance was also required in the case of cannabis. Because material had to be obtained from abroad, import and export licences had to be obtained. Normally, animal data would be expected from Phase I trials. Cannabis however was a 'peculiar substance' and this for once worked in its favour. It had a long pre-history of use and illicit self-medication existed within the community. For the proof of principle trials it was hoped to begin with a cross between a Phase II and III trial.⁴⁰ However, initially the MCA wanted additional animal data and evidence on further aspects of the different cannabis extracts. This was a problem as there were no facilities in Plymouth for such work. A combination of events worked to the benefit of the trials as the issue was resolved pragmatically on the grounds that GW Pharmaceuticals was to review animal studies, and widespread use of cannabis in the community made it unnecessary to repeat the work.

Cannabis posed particular concerns for obtaining trial licences. From the regulators point of view there were major concerns over the possible side-effects of cannabis. The risk of psychotic effects had always been an issue with cannabis and was a particular worry in clinical trials.⁴¹ Though clinicians were aware of a potential risk they calculated that the difference between medical dosage and recreational dosage mitigated the problem. Ziajeck described the implications.

*It's an increasing story that there is an association between psychosis and heavy illicit use. It's an association, and it may not be causative but evidence is becoming more convincing.... You can't shut your mind off to those issues but that is another reason to do a long-term study In illicit use the amount...is massive compared to licit medical use. You don't go out to get high...you try to lower the dose to avoid side effects.*⁴²

Regulators were concerned over the extract arm of the trial especially CBD which was less well known than THC. A compromise was reached. It was agreed to carry out a pilot study in Plymouth with a psychiatrist on standby.⁴³ The pilot started in Plymouth with twenty five patients who were contacted every three days in case of any psychotic episodes. No serious problems emerged.

Other ethical concerns were issues common to all clinical trials. If a test drug proved successful, and patients found it helpful, what were the ethical implications of withdrawing a drug at the end of the trial period?⁴⁴ In Zajicek's MS trial, a compromise agreement was reached to place patients back into treatment for an additional year. In the case of the GW Pharmaceuticals trials, Guy emphasized that any patient who believed that they had gained benefit during a study and who wished to continue to receive material beyond the end of the trial would be entered into a long-term safety extension. Guy explained, *'This is what politicians and ethics [committees] wanted.'*⁴⁵

Support from the Department of Health and Home Office was necessary for trials to take place on an illicit substance. Licences to possess any Schedule 1 drug for research had to be granted by the Home Office on the basis that there existed legitimate reasons for research. To be granted a licence researchers had to provide details of methodology and timescales, ethical approval and safeguards for safe custody and record keeping as well as delivery methods that allowed for controlled dosages. Twenty five licences for research projects on cannabis had been granted previously and the Home Office argued research was permissible under current mechanisms.

*Research into both cannabis and cannabinoids is possible within the existing policy and legal framework...The Home Office and the MCA look sympathetically at...research proposals and within the Department of Health we very much recognize the importance of research in this area and its potential value.*⁴⁶

It was hoped that the provision of 'good practice' for trials would speed the process of licensing and licences were granted for the trials. Clinicians spoke highly of the assistance rendered by the Home Office in licensing trials after 1997. Zajicek described the facilitation of the process,

Everyone's been fantastic. When you do this kind of stuff you've got all these hurdles to overcome. The Home Office were great. The MRC was fantastic. It was relatively easy... as people were keen that it took place.⁴⁷

The necessity of importing the drugs resulted in complications because international narcotics conventions required FDA export and Home Office import licences and both had to coincide which led to complicated logistics. But all these moves took time to initiate and co-ordinate and as discussed in chapter six this raised concerns over a long-time lag for patients. The MRC funded trials had not been developed to lead in themselves to the licensing of a cannabis-based medicine. If positive results were shown a pharmaceutical company was expected to license a related drug. This would take time. GW Pharmaceuticals had produced a therapeutic preparation in order to license it should it prove successful in trials. But what remained was the no small matter of passing that product successfully through the trials and for the drug to proceed through the UK/European regulatory system in order to see the provision of a licensed cannabis-based medicine.

Trials and their outcomes. The results and emergent issues of the clinical trials and their impact on the re-medicalization of cannabis

Both the 'proof of principle trials' and the industry trials demonstrated some degree of success and they showed few side-effects and some benefits. But they also highlighted a number of emergent issues associated with clinical trials in general, and some that were particular to the study of cannabis in the clinic.

One of the main problems was the issue of recruitment. The first hurdle for the trials was to obtain the patient numbers required to run a large clinical trial: a necessity to overcome the criticisms over the evidence-base resting only on small-scale studies. Recruitment problems stopped one trial from starting. CANPOP had aimed to investigate acute pain relief following tonsillectomy or abdominal surgery.⁴⁸ CANPOP suffered serious recruitment problems and was closed in October 2003 after only six patients had been recruited and randomized.⁴⁹ The sample did not provide enough information to perform a statistical analysis. Issues of recruitment, often an

issue with clinical trials, posed special problems for a study of cannabis. Recruitment appeared subject to fluctuating public perceptions of the benefits versus the risks of cannabis.⁵⁰ Holdcroft complained later, *'recruitment was so dependent on the media. If the media said something awful on recreational use we didn't get people on the trial.'*⁵¹ Holdcroft commented on frequent media reports linking cannabis use to mental health problems and she recalled, *'lobbying from the psychiatrists emphasised the bad effects. It was this, the media picked up on. These reports used to come at regular intervals.'*⁵² The media has been noted as presenting an oversimplification of cannabis issue that polarised a highly complex issue and distorting appraisals of risks.⁵³ Perceived medical problems attributed to recreational use impinged on clinical trials of therapeutic cannabis.

This problem was especially significant in the area of pain where there was a desire to recruit 'naïve patients'. Previous trials had focused on 'cannabis aware' patients in order to overcome prescription problems but this in turn had caused problems due to lay knowledge and the ability of the patient to co-operate in placebo-controlled trials. Discussion with the MRC during protocol design had meant that trials focused on the provision of the drug to 'naïve' patients after surgery. Using drug-naïve patients was seen as advantageous in that it provided better compliance with study requirements but such patients proved harder to recruit.

Retention posed further problems in the CANPOP trial as patients that agreed to take part initially dropped out after surgery. Holdcroft described the problems with consent.

*The trial had significant technical problems... they (MRC) said .. had to be assessed on its(cannabis) own without any other drug and with someone in moderate pain....this led to ethical questions... Should we not be using it along with the opiates? We had to take consent prior to someone entering study...in the cold light of day they could decide whether they wanted to be in moderate pain or not.....so we had to consent a large number of patients who never did the study as...they could not take the oral medicine.*⁵⁴

Thus the trial recruited pre-operation but, in pain after surgery, or unable to take the capsules, many of those patients dropped out of the trial. In pain treatment it was considered normal procedure to administer more than one drug, for example, in combination with the opiates. But for licensing purposes it was necessary to administer and measure only one drug: THC or an extract of cannabis. Holdcroft explained some of the problems that this approach engendered.

Drug regulatory agencies only compare and consider a drug for licensing if used on its own ... If we use ibuprofen and morphine separately they do not provide as much pain relief... they enhance each others effect.⁵⁵

Holdcroft's initial patient in the trial in 1995 used cannabis to reduce the amount of morphine required. But in the later trials cannabis had to be studied in isolation, which was in contrast to most pain management procedures. Trial design, which was designed to suit regulations, therefore failed to trial one potential cannabis application.

When the trial closed early through to lack of recruitment, Holdcroft retained funding allocated for the main trial and she intended develop methodology for a new trial. But in the intervening period the medical environment changed. For instance, technological advances in surgery reduced the intrusiveness of surgery and resultant pain. Furthermore, the failure of the first trial had led to MRC concerns about funding another. Holdcroft commented on the MRC's decision,

Having got the money, the MRC...decided not to do it. The money went back to the MRC. They thought it had taken too long and that perhaps it was not worth the money. We started with 4 hospitals. In the end we had over 20... so we had all these ready to start, then the MRC pulled the plug.⁵⁶

The failure of the first trial and loss of momentum weakened the pressure for additional trials in acute pain and interest swung away from acute to chronic pain.⁵⁷

The study of cannabis for chronic pain posed other problems. Because of the regulatory process it was necessary to test the drug for chronic pain for one disease, it could not be tested for chronic pain generally. This led to a guessing game over the

choice of illness to test, not to mention the unknowns around long-term treatment for a chronic condition. Holdcroft explained the concerns with the investigation of cannabis for chronic pain.

*It has to be licensed for a certain sub-group of patients. It's like guessing who will benefit from it more. It can't be licensed for chronic pain, it has to be for a specific incidence e.g. pain with stroke. I have concerns about long-term effects. there are no studies on long term usage and dosage.*⁵⁸

Though the main trial did not proceed, the interest in acute pain did yield some useful results. An aim of clinical trials had been to determine dosages and a dose escalation section of the trial was run successfully.⁵⁹ This was a non-randomized dose-finding study to determine the dose of cannabis needed to achieve analgesia for post-operative pain in the main randomized trial. The study identified a dose of cannabis plant extract that could provide pain relief and possible therapeutic benefit and the trial researchers reported positive results on dosage in 2006.⁶⁰

Issues of recruitment were less of a problem for the MS studies but the time it took to recruit meant that clinical trials were long-term projects. A subsequent trial on MS, CUPID, took two years to recruit the full cohort of patients. The CAMS (Cannabinoids in MS) trial began in 2001 with 667 patients. Recruitment was an issue with the CAMS trial but not to the same degree as CANPOP. Unlike the CANPOP trial Zajicek found patients happy to take part in the trials, and less scared off by adverse media reports.⁶¹

Retention posed particular problems for the study of cannabis and MS. Long-term trials for a progressive disease posed a particular set of problems. Zajicek highlighted problems. *'It remains difficult to keep people on studies if they think they are getting worse, even if (we) think the line (of progression) is less worse.'*⁶² This led CAMS trial clinicians to improve measurement instruments in order to obtain statistically significant results in a shorter timescale and these were adopted for a follow up trial, CUPID.

Lay knowledge of cannabis also posed unusual and major problems for the trials. A problem faced by clinical trials in general has been that patients often desired to have

the active drug not the placebo. This posed a particular problem with the cannabis trials. Lay knowledge meant patients were not 'blind' but rather became aware of which drug they were given in the trial and this posed two problems for the trial. Benchmark clinical trials were generally expected to be double-blind. This requirement posed a particular threat to cannabis trials. It was unusual to test a new drug about which patients already possessed a good deal of knowledge and with which they may have been self-medicating with the herbal product. Patients were able to anticipate and recognise the side-effects of cannabis and tended to work out whether they were on the active drug or the placebo. It was possible for knowledgeable pro-active patients to take the drugs and have them tested for the active ingredients. Zajicek recollected '*one patient got the pills assayed for THC and found they were on placebo. People knew what they were taking.*'⁶³ The problem was compounded because cannabis was readily available on the black market, Zajicek commenting that it was '*more difficult to do long term trials if there are other sources.*'⁶⁴ This alternative availability encouraged some patients to drop out of the programme. It also caused problems for gaining statically significant results and opened the door to criticisms over trial evidence in relation to the trials validity. A major issue with any clinical trial is the placebo effect and unblinding, and the cannabis trials were no exception. Trials on cannabis were criticized on the grounds on these grounds as well as and efficacy. The report of the MCA on the GW trials highlighted some of the issues.

*The fact that a substantial proportion of patients had previously taken illicit cannabis as self medication increases these concerns, firstly, because this may have enabled them to recognize Sativex by its psychoactivity, and secondly because they might have greater expectations of benefit from Sativex treatment than would cannabis naïve patients..... differences from placebo on efficacy measures were small and there was concern that such differences could be accounted for by unblinding and measurement bias.*⁶⁵

Patient selection became important. Patients wanted the active drugs. This knowledge had led to issues of patient selection and raised the concept of 'good patients.' CAMS clinicians found it important to select patients who were prepared to take part in a test. and they attempted to weed out patients who merely wanted access to cannabis. The problem had its humorous side as Zajicek commented on the selection of patients,

*‘most clinical trials have dropouts – few trials with dropins.... It’s about patient selection. It important to choose people who do not behave badly’.*⁶⁶ The problems led some researchers to question the importance of the concept of unblinding in clinical trials. Zajicek argued unblinding was not so important in the instance of the MS trial and argued *‘if we can prevent patients becoming wheelchair-bound people aren’t going to complain about some degree of unbinding’.*⁶⁷ The MHRA appeared to accept this compromise to a degree. In response to a similar problem in the GW trials it commented that unblinding was not a major concern in the face of a compelling treatment.⁶⁸ The importance of unblinding appeared to be related to the efficacy of cannabis-based drugs, but proving efficacy was the biggest stumbling block for the trials and to the re-medicalization of cannabis. Steering cannabis into clinical trials was one thing, proving it was a valuable treatment for MS and pain was quite another. The CAMS trial, for example, reported a very small improvement in scores for all three treatment groups, and these improvements were slightly greater in the cannabis groups than the placebo group. However, none of these changes reached statistical significance. Results were published in the *Lancet* in 2003 and the study was criticized for similar reasons to the GW trials including unblinding, placebo effect, and efficacy.⁶⁹ But was cannabis not efficacious or were clinical trials not effectual in measuring cannabis’ effect?

Efficacy proved difficult to show partly due to the outcome measures and the instruments used to test them as specified in the protocols. This was compounded by the nature of the disease under study. Holdcroft summed up the problem,

*MS has been seen as the most acceptable disease in the UK for trials of cannabinoids. Unfortunately there are probably few diseases that are harder to conduct clinical trials on.*⁷⁰

The choice of disease under test was a problem as the symptoms proved difficult to measure. A pre-determined outcome measure is specified in a trial protocol and was expected to provide objective measurement: an instrument against which success or failure is measured. A major hindrance to these trials was the problematic outcome measures in existence for MS, and pain. A point in favour of the investigation of

cannabis for MS was the fact that MS had a raft of symptoms, and cannabis it seemed might have a raft of possible impacts on the body. Robson explained the impact of cannabis' properties.

One of the great strengths of cannabis is its breadth of effect against a range of symptoms....in the beginning we triedto demonstrate that breadth of effect as one of the major assets of the drugs....Unfortunately, the more you spread your target in a clinical trial the harder it is to get a statistically significant result. Also, because of the standard way of doing things in regulatory authorities... they are looking for specific indications of drugs... ..the nearer you can get to a magic bullet the better. Cannabis is not a magic bullet. That breadth of effect which is so valued by patients with multi-symptom disease such as multiple sclerosis or HIV/AIDS has been a handicap in getting it through the trials.⁷¹

This breadth of effect was one of the reasons Paton had been wary earlier of cannabis as a therapeutic as opposed to its use as a lead.

The lack of subtle outcome measures may have contributed to a failure to prove usefulness to the extent required by clinical trials. Both GW Pharmaceuticals and the Zajicek trials used the Ashworth Scale for measuring spasticity. It was a widely used scale because it was relatively simple and allowed for ease of reproducibility in experiments. The trials cast doubt on the measure's usefulness. Zajicek later commented,

Measurement methods are not subject to scrutiny or if they have been they have fallen below acceptable levels... If we had a decent symptom measure for example in cannabis, they would probably all be licensed.⁷²

The scales lacked sensitivity especially over a short time-span. Zajicek elaborated further on the lack of sensitivity of instruments that were available for the initial trials.

The problem is that particularly in progressive disease we don't have the measurement instruments that reliably detect potential small levels of change, but levels that might be important to individuals, we don't have the sensitive outcome measures to evaluate the treatment. There needs to be huge improvement...⁷³

This proved a problem because the scales could not detect change over a short space of time, and this in turn impacted on recruitment and retention. Zajicek explained.

*The standard measurement is an awful measure. In order to see change you need three years....deteriorating people don't want to stay in the study.*⁷⁴

The patient perspective however showed the trials to be more successful than the outcome measures indicated. Listening to the patient experience the clinicians hoped that they were onto something, despite the ambivalent results which would not have satisfied regulators. Zajicek recalled the disparity between results and the patient experiences.

*Patients were rating that they found significant effects..... The bottom line was the primary outcome measures.... that study was not regarded as sufficient proof to use or license. We were left there with patients believing that the drug worked.*⁷⁵

The dichotomy between the patient experience and the results as demonstrated by the outcome measures caused clinicians to extend the trial for a further twelve months. This trial extension brought some of the first statistically significant results and ones that corresponded with new developments that had emerged from the laboratory in the 1990s on the role of cannabinoids in neuroprotection.

*Patients were followed up from the CAMS study for 12 months.....After 12 months we started to see positive results in the Ashworth score and other outcome measure of disability... Rivermead mobility index..... Over a year, we saw a spreading out of symptom benefit to other symptoms, like fatigue. To me this was very exciting but people took it with a pinch of salt... But the suggestion was, there was something there.*⁷⁶

The results from the trial extension were seen as sufficiently promising to warrant a further trial on a new application of cannabis-based medicine; one that intended to overcome earlier criticisms, making trials longer and incorporating the new methodologies. Clinicians aimed not only to show symptom relief but raised an exciting new possibility and one which was in line with new laboratory research after the discovery of the endocannabinoid receptor system; that THC, might slow the

development of disability in MS. To this end a new trial was developed called CUPID. (Cannabinoid Use in Progressive Inflammatory Brain Disease) funded by the MRC at one and a half million pounds and another one and half a million pounds was provided by a mixture of funding from the Plymouth Medical School, the MS Society and the MS Trust.⁷⁷

Supply of cannabis-based products for the trials provided an ongoing problem. Reliance on a free industrial source of synthetic THC initially posed problems for the continuation of the CAMS trial and then for the CUPID trial, with acquisitions and mergers breaking the supply of Marinol. UNIMED which had provided the THC, to the initial MRC trials was bought out by the pharmaceutical firm, Solvay. It appeared that Solvay may not have been aware of the agreement with UNIMED when they bought the company.⁷⁸ After discussion with the clinical trials team, Solvay and the MRC turned what had been a gentlemen's agreement into a firm contract intending to secure long-term supply.⁷⁹ Solvay provided further funding to increase monitoring of the trial in case it proved possible to move to licensing if there was a successful outcome. *'MRC trials tend to be proof of principle and the science level of monitoring less than in industrial.'*⁸⁰ But with the CAMS trial results ambivalent Solvay lost interest in the research and would not supply the CUPID trial. They were more interested in a small study related to migraine than work with the more complex MS.⁸¹ However, one of the employees, George Cattier who had previously worked for UNIMED, moved on to set up his own company, Insys. He agreed to provide the THC free of charge and he increased monitoring in the hope of moving towards licensing, if trials proved successful. Contracts were drawn up more tightly this time with the aid of the MHRA. The supply of cannabis extract was less complicated. The German charity which had undergone a name change to IKF agreed to continue supply and they set up their own separate substantial UK based commercial trials on MS symptom relief.

New methodologies were developed. Zajicek and others began work on new outcome measures and borrowed methodologies, which included patient questionnaires, from the social sciences. Other new technological developments were brought into the trials. In CUPID, a host of other measurements including scanning and a new spasticity

scale were added to the trial protocol. The new scale aimed to split the concept of spasticity into separate entities including: symptoms; psychological effects; and the effect on movement and mobility.⁸² Zajicek argued that the trial was important for its methodological breakthroughs.

*Even if the drug does not work it will be a really important study in terms of the methodology... we will be able to look at which bits of the measurement instruments are effective.*⁸³

In summary trials had been slow to start and the results somewhat ambivalent, however, they had been promising enough to warrant further large-scale, longer term trials and they also yielded outcome measures that it was hoped might stand a better chance of capturing cannabis' effects and enable clinicians to demonstrate efficacy. Crucially, they showed cannabis had few adverse side-effects, one of the primary fears around cannabis. The licensing of any cannabis-based medicine was left to industry.

The GW Pharmaceuticals trials had been designed with the aim of bringing a drug to market. Phase I clinical trials began in late 1999 proceeding to Phase III in 2001, on patients with MS and neuropathic pain and in 2002 pain associated with cancer. The proof of principle trials had concentrated on THC in the form of Marinol which was already licensed for another application. The process of making this available for MS and pain would therefore have been simpler if efficacy was proved. However, GW attempted to license Sativex, a Cannabis-based Medicine Extract (CBME) so the route to licensing was different and more complex than for a New Chemical Entity (NCE).⁸⁴

The form of cannabis used in Sativex caused concern to the regulators. As discussed in the previous chapter, the House of Lords Committee of 2001 questioned whether the MCA was biased over this cannabis-based drug and called into question their judgement.

The MCA's decision to insist on further toxicology data on CBD could delay the production of a cannabis-based medicine by G. W. Pharmaceuticals by as much as 2 to 3 years. Were the MCA not to require further extensive toxicological studies on CBD, GW Pharmaceuticals claim that they could have a cannabis-based prescription medicine available for patients in 2003.

We note that, according to GW Pharmaceuticals, the Canadian regulatory authorities have stated that they do not require additional animal toxicology studies for CBD. We put this to the MCA, who refused to comment, we found this refusal highly unsatisfactory.⁸⁵

The problem was that GW Pharmaceuticals and the House of Lords committee argued that cannabis extracts should not be considered as a new medicine whereas the MCA was inclined to do so. Furthermore, the House Lords Committee argued that the MCA was not treating cannabis in the same manner as other potential medicines and placed undue emphasis on assuring safety to the detriment of providing a remedy for patients. The House of Lords Report explained,

We are concerned that the MCA's approach to the licensing of cannabis-based medicines, and their insistence on the provision of new toxicological data which could delay the approval of such medicines, place the requirements of safety and the needs of patients in an unacceptable balance. Patients with severe conditions ...are being denied the right to make informed choices about their medication. There is always some risk in taking any medication; patients and their doctors should certainly be informed about the toxicological concerns that the MCA have raised, but these concerns should not prevent them from having access to what promises to be the only effective medication available to them. Overall, we consider that the MCA's attitude means that cannabis-based medicines are not being dealt with in the same impartial manner as other medicines.⁸⁶

The MCA denied any bias. But in the following year GW struggled to move Sativex through the licensing process. In 2003 GW submitted its licensing or marketing authorisation application MHRA. It was refused in 2004. The MHRA decided not to license Sativex in the UK as the Committee on Safety of Medicines was not satisfied with the efficacy of Sativex in the indication sought by the company stating that,

In reaching its advice the Medicines Commission...considered all the scientific data and arguments presented, and concluded that that the evidence of efficacy was insufficient to support granting marketing authorisations.⁸⁷

Sativex was rejected not on grounds of safety, but on failure to detect useful effects. Concerns included the small-scale nature of the trials in comparison to most other

commercial clinical trials, whether the trials were adequately blind, and whether the trials showed any statistically significant effect.⁸⁸

But the patient experience had called this assessment into question. As discussed in chapter six, the patient community greeted the refusal of Sativex in the UK with disappointment. Commenting on the MHRA's decision not to grant a licence, Mike O'Donovan, chief executive of the Multiple Sclerosis Society, expressed the belief that there was enough evidence that Sativex could alleviate spasticity.⁸⁹ Proving efficacy was reliant on the outcome measure and the patient perspective appeared to be sidelined by the measures upon which the decision was based. O'Donovan placed pressure on the Medicines Commission, which advised the MHRA, to be more flexible and he placed greater emphasis on patient relief.⁹⁰

However, though not approved in the UK, these clinical trials showed serious progress for re-medicalization. Iverson stated, '*the results with Sativex are clearly an important advance in the modern clinical development of a cannabis-based medicine.*'⁹¹ The trials resulted in the first licensing of a cannabis-based drug based on an extracts of cannabis in April 2005 when GW received regulatory approval for Sativex® from Health Canada for the symptomatic relief of neuropathic pain in Multiple Sclerosis later extended to adjunctive analgesic treatment in patients with advanced cancer. It attracted Big Pharma in the form of Bayer AG (later Bayer HealthCare) to enter into a strategic alliance with GW. Marketing of this new drug was critical. Drugs such as nabilone had struggled to establish themselves partially through limited marketing. GW announced that exclusive commercialization rights for the drug in the UK had been licensed to Bayer AG. This agreement also provided Bayer with an option to expand their licence to include the European Union and other world markets.

But the licensing process proved more difficult in the UK. In 2005, GW Pharmaceuticals unsuccessfully appealed against the advice given by the Committee on Safety of Medicines to the MHRA but the MHRA agreed with the Committee and requested further clinical efficacy data.⁹² However a system existed in the UK whereby drugs could be exempted from the licensing system and prescribed on a named-patient

basis. Although Sativex was not licensed in the UK it was issued to patients who had been in trials on a compassionate basis. After Sativex was licensed in Canada, and under pressure from both patients and doctors, the Home Office and the MHRA allowed the import of Sativex as an unlicensed medicine to be supplied on an individual patient-basis for MS on a doctors' responsibility.⁹³ A GW press release in 2005 announced,

*GW announces that it has been informed by the Home Office that the Drugs Minister, Paul Goggins, has confirmed that Sativex® oromucosal spray, its cannabis-based medicine, may be imported from Canada to satisfy its prescription to individual patients in the UK as an unlicensed medicine. This development is in response to enquiries from a number of UK doctors and individual patients who have been in contact with the Home Office to request access to Sativex.*⁹⁴

The named-patient basis was a system used to provide off-licence drugs to particular patients and was most commonly used in oncology. This situation brought additional meaning to cannabis' borderline position, not quite approved, but sufficiently approved to permit its importation for use on a named-patient basis and provided a 'wedge' between a legal and illegal drug. Professor Holdcroft summed up the resultant situation.

*What I'm not sure is why the legal side hasn't changed for medical cannabis. Guy used a wedge through..the named-patient basis. But it (Sativex) is quite expensive, not used everyday.*⁹⁵

The Home Office granted GW Pharmaceuticals a licence that permitted the company to import a product that contained a substance controlled under the Misuse of Drugs Act. Lack of efficacy was not considered grounds to refuse importation though the responsibility rested on the prescriber.⁹⁶ Whilst Marinol had also been available on a named-patient basis, Sativex became more widely used and was issued to over one thousand patients by 2006.⁹⁷

In order to have the product licensed in Europe, GW Pharmaceuticals resubmitted its application for Sativex in 2006 via the European Decentralised procedure of the European Agency for the Evaluation of Medicinal Products, (European Medicines Agency (EMA) since 2007).⁹⁸ The procedure involved the UK acting as the Reference

Member State (RMS) and if successful would have allowed licensing across the European Union. GW Pharmaceuticals however withdrew the application before the end of the procedure in response to requests for further data.⁹⁹ The MHRA provided regulatory guidelines to GW Pharmaceuticals for further work in order to help it succeed in another application.¹⁰⁰

But it also raised questions of the ‘rule of evidence and the role of clinical trials in licensing procedures. In 2009 Edwards summarises the dilemma,

I was wondering what the rule of evidence are... I don't necessarily believe that controlled trials are everything and sometimes persuasive evidence of another kind is there before one's eyes... there are also of course quite bogus claims made on single cases. ...I deeply respect what our patients say and I wish doctors would listen more often and more closely. But I also know that medicine was once founded on what doctors believed and patients told and that really wasn't enough. We also need the evidence of science and to control the placebo effect....I am left puzzled that the controlled trials building on the brilliant laboratory work.. hasn't had its pinnacle in the application to clinical medicine...I really would like to see more attention paid to the rules of evidence for our patients sake.¹⁰¹

Conclusion

Clinical trials have become of crucial importance in the provision of medicinal drugs in the twentieth century. Clinical trials in the UK on cannabis emerged after the convergence of interests and scientific developments after 1997: lobbying from patients; developments in the laboratory, the interest of individual clinicians; the involvement of professional bodies and the government's desire to split recreational use from medical benefits all played their part. The clinical trials that began after 2000 had major impacts on the process of re-medicalization. The trials which struggled to show effectiveness did indicate limited adverse effects and some potential benefits. Additionally, the trials highlighted problems of clinical trial methodology, both those generally associated with clinical trials and issues that were related to studying a drug that was based on a readily available illicit substance. The trials, both those by industry and the proof of principle trials, brought extracts of cannabis into clinical trials for the first time in the UK. This

had been made possible by the emergence of standardised extracts, and a sufficient and regular supply and delivery of cannabis-based medicine. Trials began to move cannabis further through the process of re-medicalization. In terms of legal provision of cannabis-based drugs the industry trials resulted in one cannabis-based drug being licensed in Canada. This was the first cannabis-based drug licensed since dronabinol (Marinol) and nabilone (Cesamet) in the 1980s. This time the new drug was based on an extract rather than synthetic THC and though no drug was licensed in the UK Sativex was made more widely available on a named-patient basis and available on the NHS. In terms of methodology, the trials led to an acknowledgement of the limitation of available methods for the measurement of symptoms and problems such as chronic pain and to the development of improved patient-based outcome measures which could in turn could lead to more successful outcomes of cannabis-based medicines in future trials. In terms of the application of cannabis the successful licensing of Sativex in Canada, and also the proof of principle trials in the UK, extended the application of cannabis beyond the anti-emetic properties accepted in the 1980s to MS and pain and possibly towards neuro-protective aspects in the future. The development of clinical trials has left various options open for licit cannabis-based medicines either through the development of existent synthetic, products or through the emergent cannabis-based extracts such as Sativex. If Sativex was to pass successfully through the licencing system there would then be questions of availability, cost and access on the NHS to be resolved.

¹ A proof of principle trial is a proof of concept trial rather than a drug licensing exercise.

² See appendix 8 for a summary of the trials.

³ See chapter one for a discussion of the history of clinical trials.

⁴ For a history of medicines regulation in the UK see appendix 9.

⁵ Healy, *The Creation of Psychopharmacy*, p. 312

⁶ Ibid., p. 322

⁷ Interview with Professor William Nottcutt, by Suzanne Taylor, 2007.

⁸ Interview with Professor Anita Holdcroft, by Suzanne Taylor 2009

⁹ See appendix 8 for a list of clinical trials.

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²⁸ Ibid.

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³¹ Interview with John Zajicek.

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Chapter Nine

Conclusion

‘MIST OPPORTUNITY - Does Sativex represent the future of medical marijuana—or the end?’¹

This newspaper headline from 2005 about GW Pharmaceutical’s cannabis-based spray, Sativex, posed an interesting question. Sativex was expected to gain a licence in Europe in 2010, and synthetic cannabis-based drugs were seeing something of a revival. But how did we get to this point from the WHO’s 1952 pronouncement that cannabis had no medical value and its removal as a medical substance in the UK in 1973, and what did it mean for cannabis, itself, as a medicine and its position in the drug control framework?

Cannabis’ role as a medical substance never disappeared entirely. Its medical role was maintained by some within the patient community and scientific research continued, albeit in very limited manner, even when its dual structure was denied by policy. During the period under study, many of the problems that had hindered cannabis’ transformation, from a drug to a medicine in the nineteenth and for most of the twentieth century, were overcome, facilitating re-medicalization.

Changing scientific knowledge contributed to a shifting environment around cannabis. Science had played a role in the post-war marginalization of tobacco, but, in contrast, science played an important role in the re-medicalization of cannabis. Medicinal chemists, pharmacologists, sociologists and psychiatrists, neurologists, and anaesthetists all contributed their expertise to the developing understanding of cannabis and to its application as a medicine. This took place within the context of the rise of more specialist disciplines, such as clinical pharmacology, psychopharmacology and phytopharmacy. Personal, and later professionalized, scientific networks pulled disparate researchers together and stimulated breakthroughs, any one of which, if missed, might have stopped re-medicalization. Major discoveries, including the

isolation of the active principle, THC, the synthesis of cannabinoids and the discovery of the endocannabinoid receptor system re-invigorated the field at critical points. The discovery of the endocannabinoid receptor system conferred legitimacy to anecdotal reports of cannabis's therapeutic use, for example, it demonstrated the importance of this system in the modulation of pain and opened up new avenues for research. Advances in other fields, such as the opiates, and cloning, also contributed to advances in understanding. In addition technical developments, such as mass spectrometry, enabled research to progress at a faster pace, and allowed for more subtle analysis in experiments. But 'blue sky' research is rare and individual and disciplinary interest was supplemented by the broader, twin needs of drug control and medical necessity.

Political and social fears over cannabis' recreational use and subsequent developments in drug control were paramount in the process of re-medicalization. In the search for solutions to the drug problem, countries, such as the UK, pursued, not a medical, but, a control-oriented approach. There was a global dimension to this, driven largely by the US. Medical utility was critical for the placement of drugs within drug control legislation, and cannabis' role as a medicine was eroded at the policy level. Though international and domestic drug control systems acted as a countervailing force against medical use of cannabis, they also provided a dual spur to re-medicalization. First, drug control imperatives directed funding to the cannabis field. Treating cannabis an illicit drug forced the need to improve the knowledge base for control purposes, pulling scarce resources into the cannabis arena. Though initial research focused on the deleterious effects, in the process of understanding the pharmacology of cannabis, research indicated some medical applications. Paton's work on cannabis' pharmacological relationship with anaesthetics indicated analgesic properties: an area investigated in-depth by clinicians from the 1990s. When scientific research emerged on cannabis' applications as an anti-nausea agent, and in the treatment of diseases, such as glaucoma, asthma and epilepsy, it began to overturn the viewpoint enshrined in policy: that cannabis' medical use was obsolete. But the question in the early 1970s was, whether, it was wise to utilize cannabis as a medical drug. In the light of its potential harms; its potential as a drug of misuse; not to mention its pharmacological complexity, researchers like Paton answered 'no'. Nevertheless by the mid 1970s

other pharmacologists were beginning to answer, 'yes', and it appeared that cannabis' potential as a medicine had begun to outweigh its possible harms. This was the case especially where there was clear unmet medical need for high profile medical problems such as in the management of cancer.

The transfer of this science to policy was enabled by the developing mechanism of expert advice via expert committees and the desire to place policy on a stronger evidence base, especially in the illicit drugs field. Cannabis's borderline position and widespread use within the community meant that considerable time was spent discussing cannabis, and the initial expert committees in the 1970s and 1980s provided early discussion of cannabis' potential as a therapeutic. The drug problem had been framed under the criminal justice system but as the limitations of this were revealed and other pressures mounted, both from the focus on civil liberties and the practicalities of implementing a penal approach, new approaches were sought. Early public reports, such as the Wootton Report, downplayed the harms of cannabis and raised the profile of the therapeutic use of derivatives of cannabis in policy circles and the public domain. The closed discussions of the ACMD sub-committees also contributed to a shift in the policy environment. As cannabis had lost its dual structure, cannabis discussions inevitably had to cover emergent therapeutic indications. The use of cannabis by critically ill patients highlighted further some of the problems of a penal response and necessitated evaluation of where responsibility for medical cannabis lay.

The UK had a more flexible attitude to the medical use of controlled drugs than the US. In the UK, for instance, diamorphine (heroin synthesised from morphine) had legal pharmaceutical status unlike in the US. Under the British system there existed medical and non-medical structure for the drug. Opium, existed under both legal proscription and medical prescription as its alkaloids, like morphine, retained their duality. Tobacco, on the other hand, moved further in the opposite direction. It had no medical value, and with evidence of harms increasingly accepted it became increasingly regulated and its cultural acceptability diminished. Cannabis, or, at least, its derivatives, retained the potential to return as a prescribed product and to regain its dual structure. In turn, this research and emerging scientific legitimacy began to influence discussion of

cannabis policy more generally. Whatever policy was to be adopted and implemented, scientific research was required. Without this driving force to improve the knowledge base, cannabis might have remained a poorly understood herbal product. The policy structures around cannabis, including the ACMD, the Home Office and the DHSS all demonstrated shifts, towards acceptance of cannabis as a medicine in some form. As cannabis began to regain medical credibility, policy-makers saw the advantage to be gained by recreating the dual role for cannabis, as it offered the opportunity to split medical from recreational use of cannabis, and in the process weaken demands for legalization.

Internationally, attitudes of the international agencies towards cannabis-based medicines underwent something of a change. Emergent therapeutic uses overturned the WHO's 1952 pronouncement that cannabis had no medical use, and, by the 1990s, the WHO began to take a softer line towards medical applications, for example, recommending the downgrading of dronabinol in the 1990s. Also, by the 1990s, the INCB had to concede some limited medical utility, if, perhaps only, to retain its authority and the integrity of the drug control framework. The stigma around cannabis was difficult to dispel as evidenced by the divisions between the UN agencies over dronabinol's placement within the UN 1971 Convention on Psychotropic Substances. Furthermore, herbal cannabis or medical marijuana, as advocated in some US states, and Canada, was in no way accorded a similar shift in attitude.

In transforming the concept of cannabis, the drug, into cannabis, the medicine, the pharmaceutical industry was fundamental. The development of cannabis-based medicines by industry appeared to offer a way of accepting cannabis' medical utility, at the same time as transferring the ownership from 'illicit' drug users to the professional medical sphere by putting into place medical and regulatory structures around cannabis-based drugs. In the nineteenth and early twentieth centuries, with the professionalization of medicine, patent medicines were sidelined and self-medication attacked. Commercial products and treatments were shifted away from the control of pharmacists and patients, towards pharmaceutical products regulated by government. This avenue was deemed acceptable by policy-makers and the medical establishment.

unlike patient attempts to self-medicate with unstandardized, herbal products. The isolation of THC encouraged the interest of pharmaceutical industry in the 1970s, which then provided the first licensed cannabis-based medicine since the removal of the tincture. Industry provided single, chemical entity synthetic drugs; chemically manipulated versions of the main psychoactive phytocannabinoids. Some of these proved to have too many side-effects and never made it to the clinic but re-stimulated academic research. Others were tested in the clinic and made the leap through the regulatory process in the 1980s though they did not reach a wide market. The drugs might have been introduced because of a focus on cancer, a high profile, and emotive disease, but with the stigma of cannabis still acting, and with strict controls and the advent of additional drugs for these applications, industry soon lost interest. The relative failure of the single chemical entity drugs left the door open for demands for herbal cannabis and the development of additional cannabis-based medicines. In the 1990s the niche, left open by synthetic cannabis-based medicine, stood ready to be filled. Cannabis therapeutics benefited from the changing structure of the pharmaceutical industry. The development of biotechnology firms to fill niche markets neglected by big pharma, allowed for the creation of a small firm, in the form of GW Pharmaceuticals, to take an alternative route to the process of re-medicalization: phytomedicine. To an extent, some of the constraints imposed by the stigma around cannabis for big pharma, were not relevant to a scientist entrepreneur, with a belief and expertise in phytomedicine.

Phytomedicine, which had originally filled the medicine chest and then been marginalised as the pharmaceutical industry developed and concentrated on synthetics, began a comeback in the late twentieth century. It provided a route to integrate user activist's demands for access to herbal cannabis, but at the same time provide a standardized and regulated medicine. The myriad of constituents found in cannabis, as in any plant, posed problems in early research, but, in later years, looked to be a key benefit. The desire to create a medicine out of herbal cannabis raised heated debate over the form to be researched, developed and licensed: Should it be cannabis; THC, or other cannabinoids, either singularly or in combination? The thesis demonstrated a shift from the search and development of single chemical entities, usually synthetics,

to a re-emergence of interest in botanical cannabis. That change was facilitated by the rise of phytopharmacy and the biotechnology industry. Close relationships between industry, academia and government proved decisive in the 1990s as evidenced by the story of GW Pharmaceuticals. Government licensed GW to develop cannabis-based medicines and it offered the long sought after domestic supply. GW was able to solve another key problem that had plagued cannabis: standardization of the raw material on an industrial scale. GW Pharmaceuticals' focus on a botanical substance, a traditional medicine, not a new chemical entity, meant that a product could be brought relatively quickly to market. This was a necessity when there was so much pressure to make cannabis available as a medicine. The relationship with big pharma was important. By the early twenty-first century, big pharma was showing an interest in the phytomedicine and a strategic alliance was formed between Bayer AG and GW for Bayer AG to market licensed Sativex medicines. The debates over form were important for the process of re-medicalization, as they impacted on attempts to draw a distinct line between recreational and medical use. Cannabis was a borderline substance but it was initially its derivatives that had more potential to be treated more flexibly. Once cannabis-based medicine extracts were introduced it could be argued that there was no further requirement for the use of herbal cannabis, which was more likely to remain static within the drug control framework.

The ability to deliver cannabis via a new delivery system was another factor in its re-medicalization. It was nineteenth century technological developments in drug administration systems that had helped marginalise cannabis, as it not water soluble, and therefore was not suitable for the new hypodermic syringe. The development of synthetic single entity chemical cannabinoids, delivered via tablet form whilst acceptable for policy, and to the pharmaceutical industry, proved less acceptable to patients, who maintained a preference for smoked herbal cannabis. In the 1990s, GW's new delivery system, an oral-mucosal spray, offered a number of advantages. It avoided smoked cannabis, a no-go for policy-makers and the medical community, and it bypassed the problems associated with oral administration that had beset the single chemical entity drugs, and provided patients with something more akin to the advantages of smoked cannabis.

Cannabis therapeutics in the UK after the 1990s would not have advanced as it did without the legitimacy conferred on the concept by influential professional bodies, such as the Royal Pharmaceutical Society and the BMA. When the BMA produced a reasonably favourable report on cannabis therapeutics, it boosted cannabis' legitimacy. This was important in the context of the power of the medical profession and the close relationship between the state and medicine. The Royal Pharmaceutical Society provided the practical framework to build on the recommendations of the BMA report and brought researchers, industry, funders and policy-makers together with one aim – to carry out clinical trials on cannabis and hopefully lead to a cannabis-based medicine. The House of Lords Science and Technology Committee brought all the stakeholders together in an open forum and helped alter the policy environment around cannabis, and, most importantly, provided the momentum to force the concept into reality.

The incentive to study cannabis as a medicine would not have taken place as it did without the role of lay knowledge. In this, cannabis' position as a botanical substance was important, as it meant that the general public had access to, and intellectual knowledge of, the drug in advance of it becoming a pharmaceutically produced product, in contrast to most other medicines. Despite increased controls on drugs there remained widespread illicit access to cannabis and a battle over the 'ownership' of cannabis emerged. Lay knowledge of cannabis drew attention to its medical properties for a raft of problems including; use as a palliative in the 1970s, for glaucoma; for AIDS in the 1990s, and also for MS and pain. Knowledge of cannabis' therapeutic qualities, combined with the illegal status of cannabis, led to the development of lay advocacy. Medical arguments emerged as a component of the 1960s legalization activism but, in the UK, medical activism for research and access to cannabis for MS became important in the 1990s. High profile advocacy, combined with high profile legalization demands, that developed in this period, placed pressure on policy. The result was the facilitation of clinical trials and the incentive for the pharmaceutical industry, in the form of GW Pharmaceuticals, to risk the costs of research and development, with the stated acknowledgement by government, that if an evidence-based drug could pass through clinical trials it could be licensed in the UK. Lay knowledge and advocacy was also critical in focusing the direction of research. This included the form of

cannabis to be studied and made research into extracts of cannabis imperative. It was important in forcing researchers, industry and regulators to take account of the patient perspective, no small point in medicine. Patient experience forced researchers to re-evaluate outcome measures in clinical trials. Finally, when no drug was forthcoming after the development of trials, patient concerns contributed to the circumvention of the regulatory system by the import of Sativex, on a named-patient basis as a temporary measure.

As these driving forces coalesced they resulted in a concerted effort to place cannabis into the clinical trial system, providing the opportunity to prove cannabis' safety, efficacy and quality, as demanded by the MHRA, under the Medicines Control Act of 1968. The trials that took place demonstrated safety, if not efficacy, and the issue of efficacy, it was argued, could be related not to cannabis, but, to the very methodology of randomised clinical trials themselves. The study of plant-based products, especially, for the treatment of subjective issues like pain, highlighted the inherent problems with the methodology of RCTs and the regulatory mechanisms. Although trials in the UK and the licensing of Sativex in Canada, and its introduction to the UK on a named-patient basis, represented another step in the process of re-medicalization, it remained unlicensed in the UK. Therefore, there remained a wide gap between these developments and the provision to patients.

If Sativex passed through the regulatory systems and was made available for patients what does it mean for cannabis as a medicine or indeed cannabis itself? Will such developments be successful in re-creating the dual structures for cannabis? Will patients be satisfied with Sativex, and turn away from herbal cannabis or will Sativex not fulfill expectations and demand remain for access to herbal cannabis. The development of Sativex, also raises broader questions over the treatment of traditional knowledge, herbal medicines and raw materials and the patient experience. Synthetic cannabis-based medicines proved expensive and were used in small amounts only, so how accessible will Sativex prove to be on the NHS? Will new versions and applications be produced? Where will Sativex sit within drug regulation? What impact will developments in agonists and antagonists based on the ECRS have in future

years? What would the provision of a patient and regulatory acceptable cannabis-based medicine mean for herbal cannabis within the drug regulatory system.

By 2004 with cannabis downgraded, clinical trials ongoing and Sativex apparently set to emerge as a licensed medicine, it appeared that re-medicalization of cannabis could be achieved, without forcing a major re-evaluation of international and national policies. Re-medicalization was achieved to some extent but within constrained structures within professionalized medicine. The provision of cannabis, itself, was never really on the agenda and did not extend to giving patients 'ownership' of herbal cannabis, even on a compassionate basis, a move which would have had much greater impact on legal controls on cannabis. This opens up further questions of the role and position of herbal and traditional medicines within the medical market place and regulatory systems. The therapeutic cannabis- based medicines which emerged ultimately had little impact on the legal control of cannabis as recreational and medical use existed within separate networks within the drug control and regulatory systems. When scientific, medical and industrial networks regained 'ownership' of the medical aspects of cannabis, by the end of the period under study, the medical use of cannabis looked to be back in some forms and able to exist in both controlled drug and medicine regulations. The emphasis then shifted from the place of cannabis within therapeutics and its potential impact on drug control to the broader question of the relationship between cannabis with other drugs, both illicit and licit, and the framework of drug control and the way psychoactive drugs are dealt with in society.

Despite downgrading, cannabis' continued borderline status was about to create a backlash. Prior to downgrading concerns had been raised over the dearth of research in the addictions field on cannabis and others called for a more cautious approach and the need for additional information on such substances in light of the '*history of premature closure on social policies towards psychoactive substance our experience with alcoholic beverages, tobacco, heroin and cocaine.*'² Controversy did not evaporate but rather intensified and within four years government re-graded cannabis to Class B, on the grounds of the availability of more potent strains, and the threat to mental health. Robin Murray, Professor of Psychiatry at the Institute of Psychiatry, London,

drew attention to new evidence that heavy cannabis use appeared to be linked to serious mental illness. The government came under criticism for downgrading cannabis from the UN. The UNDOC chief, Antonio Maria Costa argued against policy reversals and the message they apparently sent to young people and he was reported as stating that countries received the '*drug problems they deserved.*' Costa argued that it was a mistake to dismiss cannabis as a 'soft' drug, a view that attracted increased attention in some sections of the media.³

The rapid fluctuations of cannabis' position as a borderline drug drew attention to the validity or otherwise of the control system. Cannabis remained 'dangerous medicine' and cannabis harms included its threat to the stability or structure of the control framework. There were calls for the entire system to be re-evaluated and comparisons were drawn between cannabis and licit drugs, like alcohol and tobacco. The subsequent disagreements between the government and the ACMD drew attention to the role of expert advice, and evidence-based policy and transparency in the decision-making process. Writers have shown how little history has spoken to policy in the drugs control field or complained about the selective use of history in its formation. A knowledge of the history of drug control policies and the substances that these policies control is important for future policy around illicit drugs and medicines. What impact the debate will have on the later stages of re-medicalization remains to be seen, as, at the time of writing Sativex, is yet to pass through the final stages of regulation to provide a licensed medical drug in the UK.

¹ D. Bienenstock, 'Does Sativex represent the future of medical marijuana—or the end?' http://www.mindifidoaj.com/forum/f16/can_sativex_brings_about_end_med-7985.html

² W. Hall, and T. Babor, 'Cannabis Use and Public Health: Assessing the Burden, *Addiction*, 95 (4) (2000), p. 488.

³ P. Johnston, 'UK 'too soft on cannabis dangers.' *Telegraph* 27 June 2006. <http://www.telegraph.co.uk/news/uknews/1522399/UK-too-soft-on-cannabis-dangers.html>

Appendix 1

Search Terms:

Boundary substance, peculiar substances, borderline substances

Cannabis

Cesamet

Charvre indiene

Dronabinol

Drug addiction

Drug control

Drug dependence

Expert advice

Hashish

Institutional histories: MRC, BMA, WHO, ACMD

International agencies, WHO, INCB, UN

Key reports such as Wootton, Brain, BMA

Lay knowledge, user activism

Licensing

Marihuana

Marijuana

Marinol

Medicine Regulation

MS Society

MS

Nabilone

Pharmaceutical industry, Pharmacy, Biotechnology, Pharmaceuticals

Phytomedicine

Pot

Psychopharmacology

Regulation

Sativex

Synergism

THC

Terms were expanded as new areas of investigation emerged such as clinical trials and standardization.

Appendix 2

Re-Medicalizing Cannabis: Science, Medicine and Policy, 1960s-2003.

Principal Investigator: Professor Virginia Berridge.

Research Assistant: Ms. Suzanne Taylor: Tel: 07801365546/ suzanne.taylor@lshtm.ac.uk

**Centre for History in Public Health, London School of Hygiene & Tropical Medicine,
University of London, Keppel Street, London, WC1E 7HT.**

Cannabis has been the subject of much policy and public attention in the last few years and the recent legal changes under the Misuse of Drugs Act in the UK have been widely, although incorrectly, presented as liberalisation or legalisation of the drug. Reports of potential therapeutic uses, especially for MS and cancer chemotherapy patients, possible harmful effects, in particular, psychosis, and fluctuating government policy, have all have brought cannabis more into the media and public discussion.

Historical work on cannabis exists and has been used to inform current debates. Such history has tended to concentrate on the nineteenth century, on literary or alternative uses of the drug. Recent work has expanded our knowledge of colonial production and supply and initial international controls and many popular histories have been written contributing to the legalisation/ prohibition axes of public debate. But, the contemporary history of cannabis has been little studied. This study is framed as a history of science and policy making with the overall hypothesis that the medicalisation of cannabis has been an important route for changes in the environment in which policy on cannabis has been made. By medicalisation, or rather re-medicalisation, it is meant the introduction of medical uses and structures for the drug, as distinct from non-medical, illicit usage.

The purpose of this research project is to study the process of medicalisation of cannabis since the 1960s and the interests involved, in particular, the role of scientific research and allied professions; of industrial interests; and of user activism. The project examines the interaction of science and medicine with policy at the national level and assesses the overall impact of medicalisation on the policy environment. A key part of the research is a series of interviews with 'key informants' with views on the therapeutic use of cannabis. These interviews will feed into articles for publication in a range of health/medical and historical outlets as part of a three year Wellcome Trust funded study.

Your involvement.

I hope that you will agree to be one of the 'key informants' for the research. The interview can be as long or as short as you like. It will be conducted by Professor Virginia Berridge, an historian with long experience of the drugs and alcohol field and health research in general, or Suzanne Taylor, her Research Assistant, a medical historian with particular interest in plant-based medicine. If you would like this interview to be on a confidential basis, for background only, then please indicate this on the attached form. All interviews will be anonymised for publication if the interviewee wishes.

Storage and ethical approval.

Data will be kept in a locked filing cabinet and if material is held on a computer this will be password protected.

The study has been approved by the LSHTM Ethics Committee.

Appendix 2

Consent Form: Re-Medicalizing Cannabis: Science, Medicine and Policy, 1960s-2003.

Names of investigators:

**Principal Investigator
Research Assistant**

**Professor Virginia Berridge
Suzanne Taylor: Phone: 07801365546
Email: suzanne.taylor@lshtm.ac.uk**

**Centre for History in Public Health, London School of Hygiene & Tropical
Medicine, University of London, Keppel Street, London, WC1E 7HT.**

The purpose of this form is to allow the use of your interview for research purposes.
Please fill in the form according to your wishes.

I hereby assign copyright of my contribution for research purposes to the Centre for
History in Public Health at LSHTM.

Name:

Signature:

Date:

I permit the use of my name with quotations from the interview. []

I wish to be consulted before publication of named quotes . []

I wish quotes to be used anonymously and for background only. []

Appendix 3

Brief History of Drugs Legislation

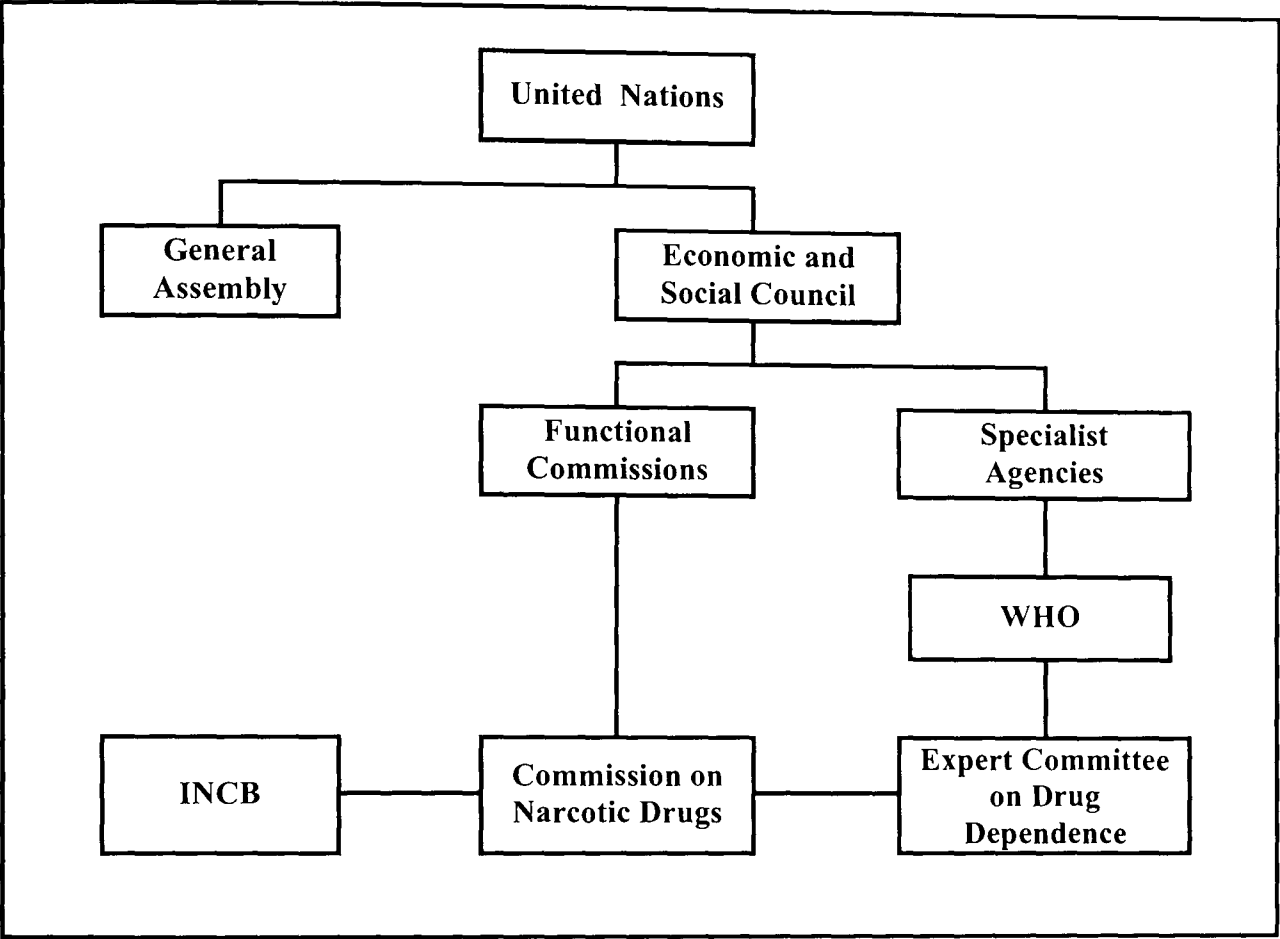
Year	International	UK Legislation	Effect
1868		Pharmacy Act	Included schedule of 15 'poisons' of which sale or supply to be restricted to pharmacies. Included opium, strychnine, belladonna and mercuric chloride.
1875		Food and Drugs Act	Penalties for adulteration
1908		Poisons and Pharmacy Act	Revised schedules of 'poisons' and 'listed sellers' of non-medicinal poisons; limited companies controlled. Added further controls over the sale of opium and morphine.
1912-1914	Hague Convention		Require parties to suppress production and trade and prohibit import and export of raw and prepared opium.
1925	Geneva Convention		Cannabis incorporated into international legislation. It did not prohibit domestic cultivation, production or distribution of cannabis.
		Dangerous Drugs Act	Controlled import and sale of addictive drugs, notably opium, cocaine and cannabis.
1933		Pharmacy and Poisons Act	Amendments to 'poisons' schedules and rules for labelling, packaging and selling medicines containing 'poisons'.
1941		Pharmacy and Medicines Act	All active ingredients of medicines for sale to be disclosed on labels; list of diseases for which advertising of medicines to treat made illegal; stamp duty repealed.
1961	UN Single Convention on Narcotic Substances		Maintained and strengthened existing controls. Extended controls to cover the plants cultivated to product narcotic drugs. Limited to medical and scientific purposes, with a 25 year exemption for traditional use. Introduced 4 schedules to classify drugs.
1964/65/67		Dangerous Drugs Acts	Extended controls to cannabis and coca leaves, effected controls over LSD, and introduced police powers of stop and search.

Year	International	UK Legislation	Effect
1968		Medicines Act	Consolidated list of diseases for which advertising to the public is illegal; medicine subject to safety quality and efficacy criteria before marketing authorisation graded three classes of medicine established, only general sales lists allowed to be sold from any shop.
1971	UN Convention on Psychotropic Substance		
		Misuse of Drugs Act	Consolidates existing law and developed the term 'controlled drugs. Introduced new drug offences including possession with intent to supply, and extend the range of controlled drugs, increased penalties for possession, and allowed for future amendments. Regulations allowed modifications to the Act. Established the Statutory advisory committee the ACMD. Included a provision for the Home Secretary to encourage research into controlled drugs.
1973		Regulations of the Misuse of Drugs Act	
1985		Controlled Drugs Penalties Act	Increase maximum prison sentences for trafficking of Class A drugs
2003		Criminal Justice Act	Makes procession of cannabis or cannabis resin an arrestable offence to co-inside with the downgrading of cannabis from Class B to Class C and increased maximum penalties.

Amended from M. Jepson, 'From Secret Remedies to Prescription Medicines: A Brief History of Medicine Quality,' in Anderson, S., *Making Medicines* (Pharmaceutical Press: London, 2005), pp. 228-229 and Jason-Lloyd, *Misuse of Drugs: A Straightforward Guide to the Law* (Waterside Press, 2007), pp. Appendix 2.

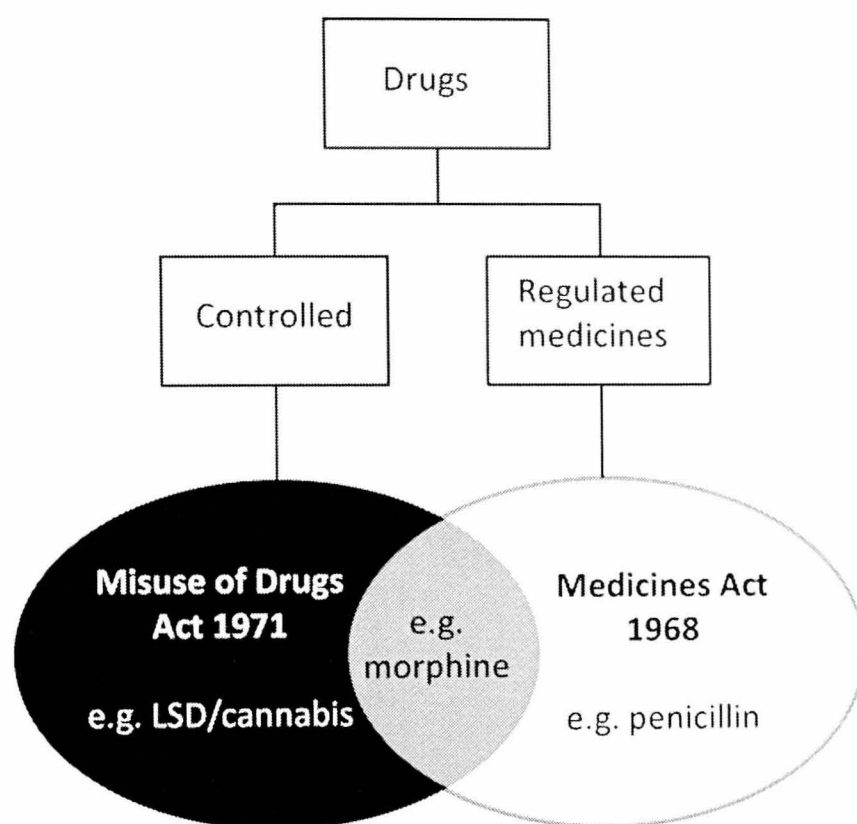
Appendix 4

United Nations system and drug control organs and their secretariat



Appendix 5

Regulation of substances 1971



Appendix 6

Prescribing of Cannabinoids

	<i>Commercially available</i>	<i>Licensed for use in UK</i>	<i>Subject to Misuse of Drugs Act (and current status)</i>	<i>Basis of use in UK</i>
<i>Nabilone</i>	Yes	Yes	No	A GP can prescribe but accepts responsibility for use for any unlicensed indications.
<i>Dronabinol</i>	Yes (USA)	No	Yes (Schedule 2) as is morphine	A GP can prescribe on a named patient basis but accepts responsibility for its use. No need for licence for clinical trials.
<i>Cannabinol</i>	No	No	Yes (schedule 1)	If a commercial product became available and cannabinol was rescheduled to Schedule 2, a GP could prescribe but accepts responsibility for use on a named-patient basis.
<i>Cannabidiol</i>	No	No	No	If a commercial product became available and was licensed, a GP could prescribe. No rescheduling is necessary.
<i>Sativex</i>	Yes (Canada)	No	?	It is available as an unlicensed medicine on a named patient basis. Currently proceeding through regulatory mechanisms in Europe.
The two compounds that are not commercially available are included to illustrate the following points :				
i	If Cannabinol was to be introduced as a commercially-available licensed product, then it would require to be moved from Schedule 1 to Schedule 2			
ii	Cannabidiol is not included in the list of substances and products listed in Schedule 1			

Amended from the House of Lords Select Committee on Science and Technology Committee, *Cannabis: The Scientific and Medical Evidence: Evidence* (London: TSO, 1998), p. 293.

Appendix 7

Expert Committees

Year	Acts	Expert Committee	Sub committees	Reports
1958		Interdepartmental Committee on Drug Addiction (ad hoc committee) (chaired by Russell Brain).		
1959				
1960				Ministry of Health Scottish Home and Health Department, <i>Drug Addiction (The Brain Report)</i> (London: HMSO, 1961).
1961				
1962				
1963				
1964				
1965				Ministry of Health Scottish Home and Health Department, <i>Drug Addiction: The second report of the Interdepartmental committee on drug addiction</i> (London: HMSO, 1965).
1966		Advisory Committee on Drug Dependence (ad hoc committee) →		
1967			Hallucinogens Subcommittee Chaired by Lady Wootton→	
1968				Advisory Committee on Drug Dependence, Hallucinogens Sub Committee, <i>Cannabis: Report by the Advisory Committee on Drug Dependence</i> (London: HMSO, 1968).
1969				
1970				

Year	Acts/bill	Expert Committee	Sub committees	Reports
1971	Misuse of Drugs Act			
1972		ACMD →	Working Group on Cannabis→	
1973				
1974				Advisory Council on Drug Misuse, First Interim Report of the Working Group on Cannabis (London: Advisory Council on the Misuse of Drugs, 1982).
1975				
1976				Advisory Council on Drug Misuse, Second Interim Report of the Working Group on Cannabis (London: Advisory Council on the Misuse of Drugs, 1982).
1977	Criminal Law Bill		ACMD: Technical Committee; Working Group on Cannabis; Working Group on Legal and Administrative Matters	
1978				
1979				ACMD releases recommendations
1980			ACMD Expert Group on the Effects of Cannabis→	
1981				
1982				Advisory Council on Drug Misuse, <i>Report of the expert group on the effects of cannabis use</i> (London: Advisory Council on the Misuse of Drugs, 1982).

Appendix 8.

Clinical trials on cannabis in the UK 1999-2008

Trial Name	PI	Dates	Product tested	Regulation and Marketing	Comments
CAMS: Cannabinoids in MS	Professor John Zajicek Derriford Hospital Plymouth Medical School	2001	THC (Marinol) Cannador (extract of cannabis.) Placebo.	Proof of Principle Trial	
CANPOP: Trial of Cannabis for Acute Post-Operative Pain	Dr Anita Holdcroft, Hammersmith Hospital London.		THC (Marinol) Cannador (extract of cannabis) Placebo	Proof of Principle Trial	This was planned as two stages. As dose finding study and a main trial. The main trial never took place due to recruitment problems.
CUPID: Cannabinoid use in Progressive Inflammatory Brain Disease	Professor John Zajicek, Derriford Hospital, Plymouth	2006-		Proof of Principle Trial	Planned as a three year study It began recruiting in 2006 reaching full cohort in 2008.
William Notcutt. For chronic pain conditions including MS.	William Notcutt, John Paget Hospital Norfolk		Nabilone Sativex	Proof of Principle Trial	

Trial Name	PI	Dates	Product tested	Regulation and Marketing	Comments
GW Pharmaceuticals Trials.		1999-	Cannabinoids, with a focus on Sativex (CBD and THC)	Submitted to MHRA 2003 and refused 2004. Licensed in Canada 2005 by Health Canada. 2005 Appealed MHRA decision. 2005 Made available on an unlicensed, named-patient basis in the UK. 2006 Regulatory submission to European Agency for the Evaluation of Medical Products. (now EMEA). Application withdrawn. 2009 Resubmitted to EMEA, decision expected early 2010.	

Appendix 9

A Brief History of UK Medicines Regulation

Date	Event
1864	The first edition of the British Pharmacopoeia (BP) set standards for the manufacture of common established drugs.
1917	The Venereal Disease Act and later the Cancer Act of 1939 prevented the advertising and promotion of medicines for these conditions.
1925	The Therapeutic Substances Act introduced regulations concerning the manufacture of biological substances. Consolidated 1956.
1961	The thalidomide disaster.
1963	The Committee on Safety of Drugs (CSD) established.
1967	A White Paper recommended legislation rather than a voluntary system to control medicines.
1968	Medicines Act received Royal Assent.
1971	The Medicines Commission, an expert advisory committee, created to advise Ministers. The CSD became the Committee on Safety of Medicines (CSM) and later the Commission for Human Medicines (CHM).
1989	Medicines Control Agency (MCA) created.

1995	The European Medicines Agency (EMA) was set up to co-ordinate and provide regulatory support to EU member states as was the European Medicines Advisory Committees for both human and veterinary medicines.
2003	The Medicines Control Agency and the Medical Devices Agency - merged to form the Medicines and Healthcare products Regulatory Agency (MHRA). The CSM and Medicines Commission merged to form the Commission on Human Medicine (CHM) a committee of the MHRA. The MHRA is an executive agency of the Department of Health and is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

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